

The American Journal of Cardiology[®]

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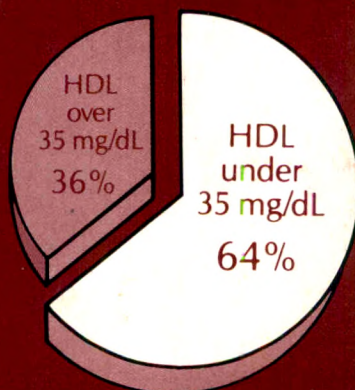
63

240_{TOTAL}
—
<35_{HDL}

Low HDL with elevated
LDL and triglycerides:
A common denominator of
many heart attack victims

Mixed hyperlipidemias—elevated cholesterol and triglycerides—are common among heart attack victims,¹ and nearly two thirds of people who developed myocardial infarction in the PROCAM Trial had a low (< 35 mg/dL) baseline level of HDL cholesterol.² LOPID® (gemfibrozil) is not indicated for the treatment of patients with low HDL cholesterol as their only lipid abnormality.

HEART ATTACK PATIENTS
(PROCAM TRIAL)²



The American Journal of Cardiology

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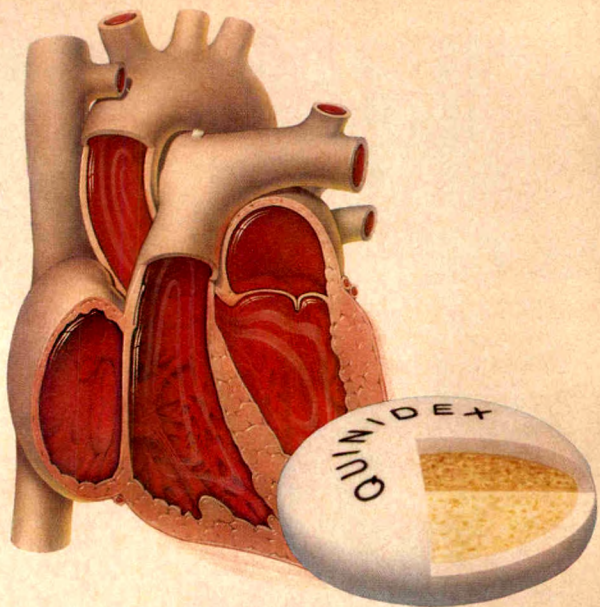
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P24,184

The following is a brief summary only. Before prescribing, see complete prescribing information in Quinidex product labeling.

Contraindications: Intraventricular conduction defects. Complete A-V block. A-V conduction disorders caused by digitalis intoxication. Aberrant impulses and abnormal rhythms due to escape mechanisms. Idiosyncrasy or hypersensitivity to quinidine or related cinchona derivatives. Myasthenia gravis.

Warnings: In the treatment of atrial flutter, reversion to sinus rhythm may be preceded by a progressive reduction in the degree of A-V block to a 1:1 ratio, resulting in an extremely rapid ventricular rate. This possible hazard may be reduced by digitalization prior to administration of quinidine.

Reports in the literature indicate that serum concentrations of digoxin may increase and may even double when quinidine is administered concurrently. Patients on concomitant therapy should be carefully monitored for digitalis toxicity. Reduction of digoxin dosage may have to be considered.

Manifestations of quinidine cardiotoxicity such as excessive prolongation of the QT interval, widening of the QRS complex and ventricular tachyarrhythmias mandate immediate discontinuation of the drug and/or close clinical and electrocardiographic monitoring.

In susceptible individuals, such as those with marginally compensated cardiovascular disease, quinidine may produce clinically important depression of cardiac function manifested by hypotension, bradycardia, or heart block. Quinidine therapy should be carefully monitored in such individuals.

Quinidine should be used with extreme caution in patients with incomplete AV block since complete AV block and asystole may be produced. Quinidine may cause abnormalities of cardiac rhythm in digitalized patients and therefore should be used with caution in the presence of digitalis intoxication.

Quinidine should be used with caution in patients exhibiting renal, cardiac or hepatic insufficiency because of potential accumulation of quinidine in serum, leading to toxicity.

Patients taking quinidine occasionally have syncopal episodes which usually result from ventricular tachycardia or fibrillation. This syndrome has not been shown to be related to dose or serum levels. Syncopal episodes frequently terminate spontaneously or in response to treatment, but sometimes are fatal.

Cases of hepatotoxicity, including granulomatous hepatitis, due to quinidine hypersensitivity have been reported. Unexplained fever and/or elevation of hepatic enzymes, particularly in the early stages of therapy, warrant consideration of possible hepatotoxicity. Monitoring liver function during the first 4-8 weeks should be considered. Cessation of quinidine in these cases usually results in the disappearance of toxicity.

Precautions: General—All the precautions applying to regular quinidine therapy apply to this product. Hypersensitivity or anaphylactoid reactions to quinidine, although rare, should be considered, especially during the first weeks of therapy. Hospitalization for close clinical observation, electrocardiographic monitoring, and determination of serum quinidine levels are indicated when large doses of quinidine are used or with patients who present an increased risk.

Information for Patients: As with all solid dosage medications, Quinidex Extentabs should be taken with an adequate amount of fluid, preferably with the patient in an upright position to facilitate swallowing. They should be swallowed whole in order to preserve the controlled-release mechanism.

Laboratory Tests: Periodic blood counts and liver and kidney function tests should be performed during long-term therapy; the drug should be discontinued if blood dyscrasias or evidence of hepatic or renal dysfunction occurs.

Drug Interactions

Drug
Quinidine with anticholinergic drugs
Quinidine with cholinergic drugs
Quinidine with carbonic anhydrase inhibitors, sodium bicarbonate, thiazide diuretics

Quinidine with coumarin anticoagulants
Quinidine with tubocurarine, succinylcholine and decamethonium
Quinidine with phenothiazines and reserpine
Quinidine with hepatic enzyme-inducing drugs (phenobarbital, phenytoin, rifampin)

Quinidine with digoxin
Quinidine with amiodarone
Quinidine with cimetidine
Quinidine with ranitidine
Quinidine with verapamil
Quinidine with nifedipine

Effect

Additive vagolytic effect
Antagonism of cholinergic effects
Alkalinization of urine resulting in decreased excretion of quinidine

Reduction of clotting factor concentrations
Potentialization of neuromuscular blockade
Additive cardiac depressive effects
Decreased plasma half-life of quinidine

Increased serum concentration of digoxin (See Warnings)
Increased serum concentration of quinidine
Prolonged quinidine half-life and an increase in serum quinidine level
Premature ventricular contractions and/or bigeminy
Increased quinidine half-life and an increase in serum quinidine level; potential hypotensive reactions
Decreased serum concentrations of quinidine

Carcinogenesis: Studies in animals have not been performed to evaluate the carcinogenic potential of quinidine.

Pregnancy, Teratogenic Effects: Pregnancy Category C. Animal reproduction studies have not been conducted with quinidine. There are no adequate and well-controlled studies in pregnant women. Quinidex Extentabs should be administered to a pregnant woman only if clearly indicated.

Nonteratogenic Effects: Like quinine, quinidine has been reported to have oxytocic properties. The significance of this property in the clinical setting has not been established.

Laboratory Tests: There is no known use for Quinidex Extentabs in labor and delivery. However, quinidine has been reported to have oxytocic properties. The significance of this property in the clinical setting has not been established.

Nursing Mothers: Because of passage of the drug into breast milk, caution should be exercised when Quinidex Extentabs are administered to a nursing woman.

Pediatric Use:—There are no adequate and well-controlled studies establishing the safety and effectiveness of Quinidex Extentabs in children.

Adverse Reactions: Symptoms of cinchonism, such as ringing in the ears, loss of hearing, dizziness, lightheadedness, headache, nausea, and/or disturbed vision may appear in sensitive patients after a single dose of the drug. The most frequently encountered side effects to quinidine are gastrointestinal.

Gastrointestinal:—Nausea, vomiting, abdominal pain, diarrhea, anorexia, granulomatous hepatitis (which may be preceded by fever), esophagitis.

Cardiovascular:—Ventricular extrasystoles occurring at a rate of one or more every 6 normal beats; widening of the QRS complex and prolonged QT interval; complete A-V block; ventricular tachycardia and fibrillation; ventricular flutter; torsade de pointes; arterial embolism; hypotension; syncope.

Central Nervous System:—Headache, vertigo, apprehension, excitement, confusion, delirium, dementia, ataxia, depression.

Ophthalmologic and Otic:—Disturbed hearing (tinnitus, decreased auditory acuity), disturbed vision (mydriasis, blurred vision, disturbed color perception, photophobia, diplopia, night blindness, scotomata), optic neuritis, reduced visual field.

Dermatologic:—Cutaneous flushing with intense pruritus, photosensitivity, urticaria, rash, eczema, exfoliative eruptions, psoriasis, abnormalities of pigmentation.

Hypersensitivity:—Angioedema, acute asthmatic episode, vascular collapse, respiratory arrest, hepatotoxicity, granulomatous hepatitis (See Warnings), purpura, vasculitis.

Hematologic:—Thrombocytopenia, thrombocytopenic purpura, agranulocytosis, acute hemolytic anemia, hypoprothrombinemia, leukocytosis, shift to left in WBC differential, neutropenia.

Immunologic:—Systemic lupus erythematosus, lupus nephritis.

Miscellaneous:—Fever, increase in serum skeletal muscle creatine phosphokinase, arthralgia, myalgia.

Twice-a-day dosing* to make life easier for your arrhythmia patients. That's the Quinidex® advantage. Because, like the heart, Quinidex Extentabs® have been uniquely constructed for dependable around-the-clock performance.

*Some patients may require t.i.d. dosing.



QUINIDEX EXTENTABS®

(Quinidine Sulfate Extended-release Tablets, USP) 300 mg

A-H-ROBINS

Pharmaceutical Division, Richmond, Virginia 23261-6609
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CORONARY ARTERY DISEASE**665****Comparison of Celiprolol and Propranolol in Stable Angina Pectoris**

William H. Frishman, Mark Heiman, Judith Soberman, Steven Greenberg, and Jack Eff, for the Celiprolol International Angina Study Group

Is once-daily celiprolol, a β_1 -selective adrenoceptor blocker with selective partial β_2 -adrenoceptor activity, safer and more efficacious than twice-daily propranolol? Both drugs were compared with placebo in this multicenter, double-blind, randomized, titration-to-effect study of 140 patients with stable, exercise-induced angina pectoris.

671**Effects of Atenolol Alone, Nifedipine Alone and Their Combination on Ambulant Myocardial Ischemia**

James A. Hill, Jose I. Gonzalez, Robert Kolb, and Carl J. Pepine

The effects of atenolol and nifedipine and their combination on ambulant myocardial ischemia were investigated in 18 minimally symptomatic men using a randomized, double-blind, placebo-controlled, crossover trial. Monotherapy with nifedipine or atenolol is similarly effective in eliminating or reducing ambulant ischemia. Combination therapy can provide additional benefit in those with continued ischemia.

676**Spontaneous Myocardial Ischemia and the Signal-Averaged Electrocardiogram**

Gioia Turitto, Edward B. Caref, Egidio Zanchi, Fabio Menghini, George Kelen, and Nabil El-Sherif

The effects of transient myocardial ischemia on the signal-averaged electrocardiogram were investigated in 13 patients with coronary artery disease and spontaneous angina undergoing 3-channel ambulatory electrocardiography. Spontaneous transient myocardial ischemia, independent of its type, location, duration and magnitude, did not generate a substrate for late potentials on the signal-averaged electrocardiogram.

681**Right Ventricular Systolic Function During Exercise With and Without Significant Coronary Artery Disease**

J. Thomas Heywood, Joerg Grimm, Otto M. Hess, Markus Jakob, and Hans P. Krayenbuehl

To evaluate the effects of exercise and coronary artery disease on right ventricular systolic function, rest and exercise biplane RV angiograms were recorded in 20 patients undergoing diagnostic cardiac catheterization. There is a decline in RV ejection fraction during exercise in patients with significant coronary

artery disease. The generalized reduction in regional RV ejection fraction coupled with the close correlation with the change in pulmonary resistance suggests that increased afterload, rather than RV ischemia, is the cause.

687**Coronary Collateral Circulation in Coronary Artery Disease and Systemic Hypertension**

Zenon S. Kyriakides, Dimitrios T. Kremastinos, Nickolas A. Michelakakis, Evangelos P. Matsakas, Thomas Demovelis, and Pavlos K. Toutouzas

Patients were studied to evaluate coronary collateral circulation in relation to the presence of systemic hypertension and left ventricular hypertrophy. Results indicate that coronary collateral circulation in hypertensive patients was more extensive than in normotensive patients with the same characteristics. The increase in coronary collateral circulation corresponded to the degree of left ventricular wall thickness in patients with systemic hypertension and coronary artery disease.

691**Results of Intracoronary Stents for Management of Coronary Dissection After Balloon Angioplasty**

Michael Haude, Raimund Erbel, Uwe Straub, Ulrich Dietz, Richard Schatz, and Jürgen Meyer

This study reports on the implantation of balloon-expandable Palmaz-Schatz stents in 15 patients with symptomatic dissection after coronary angioplasty. Intracoronary stenting appears to be a secure and effective method of handling bailout situations caused by dissection after balloon angioplasty with good long-term results when only a single stent is implanted.

ARRHYTHMIAS AND CONDUCTION DISTURBANCES**697****Reduction in the Frequency of Ventricular Late Potentials After Acute Myocardial Infarction by Early Thrombolytic Therapy**

Marc Zimmermann, Richard Adamec, and Stefano Ciaroni, with the technical assistance of Florida Malbois and Roland Tièche

To assess the effect of intravenous thrombolysis on the incidence of ventricular late potentials, 223 consecutive patients surviving a first acute myocardial infarction were studied. Intravenous thrombolysis with recombinant tissue-type plasminogen activator reduces the incidence of late potentials in survivors of a first AMI and this reduced incidence appears to be related to the patency of the infarct-related artery.

704

Late Outcome of Survivors of Out-of-Hospital Cardiac Arrest With Left Ventricular Ejection Fractions $\geq 50\%$ and Without Significant Coronary Arterial Narrowing

Peter J. Kudenchuk, Leonard A. Cobb, H. Leon Greene, Carol E. Fahrenbruch, and Florence H. Sheehan

Forty-three survivors of out-of-hospital ventricular fibrillation with minimal or no coronary artery stenoses and in whom left ventricular ejection fraction was ≥ 0.50 were evaluated. Although cardiac arrest rarely occurs in patients without major structural heart disease, its recurrence in such survivors is common. Patients at relatively high risk for recurrent VF can be identified by their youth and by abnormalities detected on the surface 12-lead electrocardiogram or by contrast left ventriculography.

709

Comparison of Clinical and Electrophysiologic Features of Preexcitation Syndromes in Patients Presenting Initially After Age 50 Years with Those Presenting at Younger Ages

Lynda E. Rosenfeld, Alice M. Van Zetta, and William P. Batsford

Of 73 patients documented over an 8-year period to have preexcitation syndromes at electrocardiographic study, 13 were >50 years old and presented in the setting of acute medical or surgical diseases, or chronic cardiac disease often associated with middle age and atrial arrhythmias. Specific age-related descriptors that characterize patients presenting with preexcitation syndromes in late adulthood may help to facilitate this often difficult diagnosis.

713

Usefulness of Flecainide for Prevention of Paroxysmal Atrial Fibrillation and Flutter

Adrian H. Pietersen and Henning Hellemann, for the Danish Norwegian Flecainide Multicenter Study Group

Is flecainide acetate efficacious in preventing attacks of paroxysmal atrial fibrillation and flutter? In this double-blind cross-over study of 43 patients randomized to receive either placebo or 150 mg of flecainide twice per day for consecutive periods of 3 months, flecainide significantly suppressed the number of attacks, with frequent but mostly tolerable adverse effects.

718

Time of Onset of Supraventricular Tachyarrhythmia in Relation to Alcohol Consumption

Markku Kupari and Pekka Koskinen

The etiology and time of onset of supraventricular tachyarrhythmia was recorded in 289 patients aged <65 years who also underwent a screening test for alcoholism and an assessment of alcohol consumption during the week preceding the arrhythmia. Among 102 patients with idiopathic arrhythmias, those with arrhythmias beginning on Saturdays or Sundays were more often chronic, heavy drinkers than either those with episodes beginning from Mondays through Fridays or control subjects from the out-of-hospital population. Although this study confirms an association between heavy drinking and idiopathic arrhythmias beginning during weekends, it shows that the question may be of a relative rather than an absolute overrepresentation.

SYSTEMIC HYPERTENSION

723

Mean and Range of the Ambulatory Pressure in Normotensive Subjects from a Meta-Analysis of 23 Studies

Jan A. Staessen, Robert H. Fagard, Paul J. Lijnen, Lutgarde Thijs, Roger Van Hoof, and Antoon K. Amery

To perform a meta-analysis of published reports in an attempt to determine the mean and range of the normal ambulatory blood pressure, 23 studies including a total of 3,476 normal subjects were reviewed. Until the results of prospective studies on the relation between ambulatory BP and the incidence of cardiovascular morbidity and mortality become available, the intervals in this study could serve as a temporary reference for clinical practice.

728

Hemodynamic and Neurohormonal Effects of Quinidine in Patients with Severe Left Ventricular Dysfunction Secondary to Coronary Artery Disease or Idiopathic Dilated Cardiomyopathy

Stephen S. Gottlieb and Michelle Weinberg

The hemodynamic and neurohumoral response to oral quinidine was determined in 19 patients with severe chronic heart failure. Vasodilation is the predominant hemodynamic effect of oral quinidine in patients with congestive heart failure. However, potential adverse effects may be caused by consequent neurohormonal activation.

732

Effects of Prolonged Infusion of Human Alpha Calcitonin Gene-Related Peptide on Hemodynamics, Renal Blood Flow and Hormone Levels in Congestive Heart Failure

Y. Chandra Shekhar, Inder S. Anand, Raghav Sarma, Roberto Ferrari, Purshotam L. Wahi, and Philip A. Poole-Wilson

The effects of prolonged infusion of calcitonin gene-related peptide on hemodynamic functions, plasma hormones and renal blood flow were studied in 9 patients with congestive heart failure. CGRP has sustained beneficial effects on hemodynamic indexes and has no adverse effects on hormones. Unlike many other vasodilators, CGRP also increases renal blood flow and glomerular filtration.

CONGENITAL HEART DISEASE

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Analysis of Survival in Patients with Pulmonic Valve Atresia and Ventricular Septal Defect

Michael Hofbeck, Jan T. Sunnegårdh, Patricia E. Burrows, C. A. F. Moes, Nancy Lightfoot, William G. Williams, George A. Trusler, and Robert M. Freedom

The clinical course of 104 consecutive patients diagnosed in the first year of life with pulmonic valve atresia and ventricular septal defect was followed for a mean of 4.95 years, with specific attention paid to the nature of pulmonary blood supply and its influence on patient outcome. Confluent pulmonary arteries supplied by a single ductus arteriosus were present in 72 patients (group I), whereas pulmonary blood supply in 32 patients (group II) depended partially or exclusively on systemic collateral arteries. Although an estimated probability of

10-year survival was 69% for the entire cohort, arborization and distribution abnormalities of the pulmonary arteries as well as intrapulmonary stenoses in group II patients accounted for their significantly lower probability of undergoing corrective surgery.

744

Pulmonary Artery Morphology and Hemodynamics in Pulmonic Valve Atresia with Ventricular Septal Defect Before and After Repair

Yasuhiro Shimazaki, Masahiko Iio, Susumu Nakano, Shizuo Morimoto, Seiichiro Ikawa, Hikaru Matsuda, and Yasunaru Kawashima

Hemodynamic measurements and the number of effective subsegments connected to the pulmonary arteries, obtained at cardiac catheterization and angiographic studies performed in 22 patients with pulmonic valve atresia and ventricular septal defect before and after surgical repair, revealed that postoperative pulmonary artery pressure and pulmonary vascular resistance may be predictable when the pulmonary artery area and the number of effective subsegments are measured before repair. Early palliation to increase pulmonary artery size and the number of effective subsegments is recommended for obtaining normal pulmonary hemodynamics after repair.

MISCELLANEOUS

749

Catheter-Based Intravascular Ultrasound Imaging of Chronic Thromboembolic Pulmonary Disease

François Ricou, Pascal H. Nicod, Kenneth M. Moser, and Kirk L. Peterson

Pulmonary thromboendarterectomy is the treatment of choice for pulmonary hypertension due to chronic pulmonary thromboemboli. Results show that intravascular ultrasound of pulmonary arteries is feasible and safe in patients with pulmonary hypertension. It may help to assess the location and the extent of the pathologic process involving pulmonary arteries.

METHODS

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Assessment of Right Ventricular Oxidative Metabolism by Positron Emission Tomography with C-11 Acetate in Aortic Valve Disease

Rodney J. Hicks, Victor Kalff, Vicky Savas, Mark R. Starling, and Markus Schwaiger

Right ventricular C-11 clearance rate constants were compared with RV loading in 21 patients with aortic valve disease to assess possible use of this technique for noninvasive evaluation of RV oxidative metabolism. Data suggest these constants were significantly higher in patients with elevated than in those with normal pulmonary artery pressures. Preliminary data suggest that RV C-11 acetate clearance rate constants can provide noninvasive assessment of RV oxidative metabolism.

758

Validity of Catheter-Tip Doppler Technique in Assessment of Coronary Flow Velocity and Application of Spectrum Analysis Method

Masakazu Yamagishi, Daisuke Hotta, Jun Tamai, Satoshi Nakatani, and Kunio Miyatake

We examined the validity of a newly developed fast-Fourier transformation analysis system by which Doppler signals from a catheter-tip probe were analyzed in a model circuit and in clinical cases. There was good correlation between Doppler-derived flow velocity and actual flow velocity both in vitro and in vivo, suggesting that the catheter-tip Doppler technique with full spectrum analysis is useful in clinically assessing coronary flow velocity patterns.

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Paul G. Hugenholtz

BRIEF REPORTS

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Effects of Superoxide Dismutase on Reperfusion Arrhythmias and Left Ventricular Function in Patients Undergoing Thrombolysis for Anterior Wall Acute Myocardial Infarction

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Variability of the QT Measurement in Healthy Men, with Implications for Selection of an Abnormal QT Value to Predict Drug Toxicity and Proarrhythmia

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Wilbert S. Aronow and Itzhak Kronzon

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Mitral Regurgitation During B Bump of the Mitral Valve Studied by Doppler Echocardiography

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Aortic Aneurysm in Patients with Functionally Normal or Minimally Stenotic Bicuspid Aortic Valve

Roman T. Pachulski, Anthony L. Weinberg, and Kwan-Leung Chan

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Effect of Cyclosporine on Plasma Endothelin Levels in Humans After Cardiac Transplantation

Brooks S. Edwards, Sharon A. Hunt, Michael B. Fowler, Hannah A. Valantine, Lisbeth M. Anderson, and Amir Lerman

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Usefulness of the Subaortic Diameter for Normalizing Left Ventricular and Left Atrial Dimensions

Michael J. Domanski, Robert E. Cunnion, and William C. Roberts

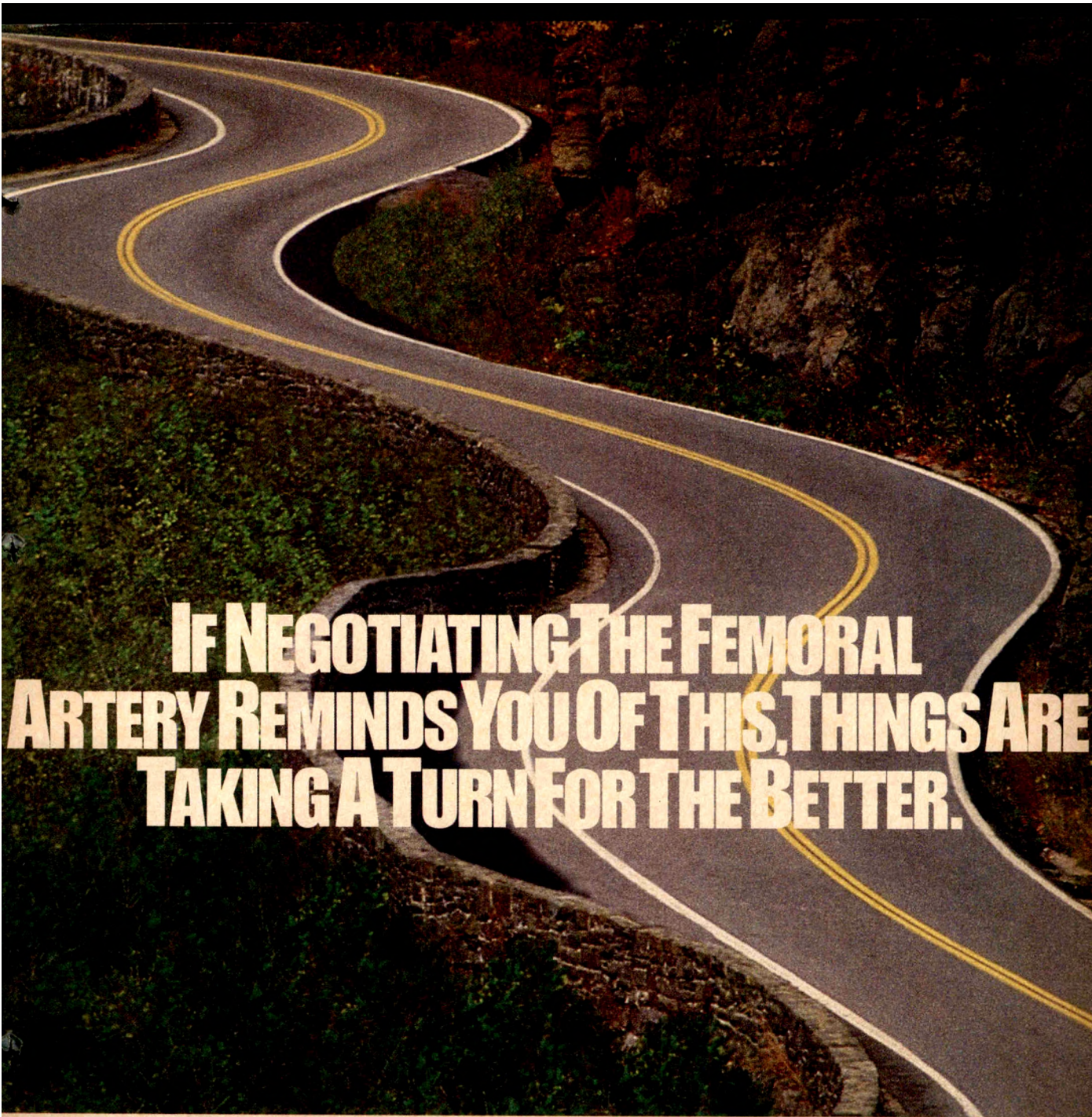
787

Complications of Diagnostic Cardiac Catheterization Requiring Surgical Intervention

Jon R. Cohen, Frederic Sardari, Lauren Glener, John Peralo, Andrew Grunwald, Gary Friedman, Jerome Koss, Obi Nwasokwa, and Monty Bodenheimer

INSTRUCTIONS TO AUTHORS on page 768

CLASSIFIED ADVERTISING on pages A60, A70, A74, A84, A85

An aerial photograph of a dark asphalt road with double yellow lines, winding through a lush green, hilly landscape. The road curves sharply to the left and then back to the right, disappearing into the distance.

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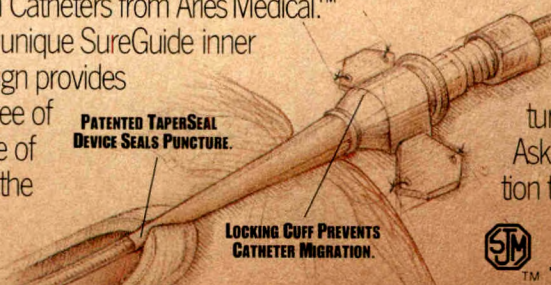
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665**Comparison of Celiprolol and Propranolol in Stable Angina Pectoris**

William H. Frishman, Mark Heiman, Judith Soberman, Steven Greenberg, and Jack Eff, for the Celiprolol International Angina Study Group

The comparative antianginal effects and safety profiles of propranolol and celiprolol, a β_1 -selective adrenoceptor blocker with selective partial β_2 -adrenoceptor activity, were assessed in a multicenter, placebo lead-in, active control, double-blind, randomized, titration-to-effect study of 140 patients with stable, exercise-induced angina pectoris. Compared with placebo baseline measurements, both celiprolol and propranolol reduced anginal attack frequency and nitroglycerin consumption, and increased symptom-limited treadmill exercise times, with no differences seen between treatments. Propranolol was associated with a lower heart rate at rest than celiprolol. Both drugs significantly reduced the rate-pressure product at the conclusion of exercise testing. Both drugs were well tolerated; propranolol was associated with more symptomatic bradycardia. Once-daily celiprolol is as effective as twice-daily propranolol in the treatment of patients with stable angina pectoris.

671**Effects of Atenolol Alone, Nifedipine Alone and Their Combination on Ambulant Myocardial Ischemia**

James A. Hill, Jose I. Gonzalez, Robert Kolb, and Carl J. Pepine

The effects of atenolol (100 mg/day) and nifedipine (20 mg twice daily) and their combination on ambulant myocardial ischemia were investigated in 18 minimally symptomatic men using a randomized, double-blind, placebo-controlled, crossover trial. Four blinded treatment periods of 2 weeks' duration (2 placebo, 1 atenolol, 1 nifedipine) were used in all patients. The 9 patients who did not have ischemia eliminated by monotherapy also received combination therapy with both drugs. Both nifedipine and atenolol as monotherapy reduced the number of ischemic episodes and the average duration of each episode compared with placebo ($p < 0.05$). Compared with placebo, nifedipine reduced the total duration of ischemia ($p < 0.05$) but the effect of atenolol on ischemia duration was of borderline significance ($p = 0.066$). There were no differences in reduction of ischemic parameters when atenolol was compared with nifedipine (difference not significant). In the 9 patients who continued to have ischemia during monotherapy, combination therapy eliminated it in 2 and

Continued on page A16

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reduced the duration by >50% in the remaining patients compared to placebo. In conclusion, monotherapy with nifedipine or atenolol is similarly effective in eliminating or reducing ambulant ischemia. Combination therapy can provide additional benefit in those with continued ischemia.

676

Spontaneous Myocardial Ischemia and the Signal-Averaged Electrocardiogram

Gioia Turitto, Edward B. Caref, Egidio Zanchi, Fabio Menghini, George Kelen, and Nabil El-Sherif

Serial signal-averaged electrocardiograms were obtained from 3-channel Holter recordings in 13 patients with coronary artery disease and spontaneous angina. Fifty-four baseline signal-averaged electrocardiograms were compared with those recorded during 54 transient myocardial ischemic attacks. Among them, 14 had ST elevation and 40 ST depression, 21 had an anterior location and 23 an inferior location, 29 had a duration >10 minutes, and 18 had a magnitude >2 mm. Baseline signal-averaged electrocardiograms were abnormal in 5 cases (38%). No significant changes were observed on signal-averaged electrocardiograms recorded at baseline and during transient myocardial ischemic attacks. Absence of significant changes was also noted when analysis was performed separately according to the type of ischemic attacks (with ST elevation or depression), their location (anterior or inferior), duration and magnitude. It is concluded that spontaneous transient myocardial ischemia, independent of its characteristics, does not create a substrate for late potentials on the signal-averaged electrocardiogram.

681

Right Ventricular Systolic Function During Exercise With and Without Significant Coronary Artery Disease

J. Thomas Heywood, Joerg Grimm, Otto M. Hess, Markus Jakob, and Hans P. Krayenbuehl

Six patients with no or only mild coronary artery disease (group 1) and 7 with significant disease (group 2) underwent rest and exercise right ventriculography. Heart rate and right ventricular (RV) systolic pressure increased substantially in both groups with exercise. Pulmonary resistance increased only in group 2 during exercise, and there was a generalized, rather than segmental, decline in regional RV ejection fraction in group 2 with exercise. A close correlation between the change in pulmonary resistance and RV ejection fraction from rest to exercise was seen. Increased afterload appears to contribute to RV systolic dysfunction during exercise in patients with coronary artery disease.

687

Coronary Collateral Circulation in Coronary Artery Disease and Systemic Hypertension

Zenon S. Kyriakides, Dimitrios T. Kremastinos, Nickolas A. Michelakakis, Evangelos P. Matsakas, Thomas Demovelis, and Pavlos K. Toutouzas

To evaluate the coronary collateral circulation in relation to the presence of systemic hypertension and left ventricular hypertrophy, 61 hypertensive patients, aged 55 ± 9 years, and 252 normotensive patients, aged 53 ± 8

Continued on page A23

years, with coronary artery disease and the same coronary angiographic characteristics were studied. Left ventricular wall thickness was 1.26 ± 0.1 cm in the hypertensive and 1.03 ± 0.06 cm in the normotensive group ($p < 0.001$). The hypertensive group had more extensive coronary collateral circulation than the normotensive group ($p < 0.01$). Coronary collateral circulation had a positive relation to left ventricular wall thickness ($p < 0.001$). These results indicate that patients with systemic hypertension and coronary artery disease have an increase in coronary collateral circulation correlated with the degree of left ventricular wall thickness.

691**Results of Intracoronary Stents for Management of Coronary Dissection After Balloon Angioplasty**

Michael Haude, Raimund Erbel, Uwe Straub, Ulrich Dietz, Richard Schatz, and Jürgen Meyer

This study reports on the implantation of balloon-expandable Palmaz-Schatz stents in 15 patients with symptomatic dissections after coronary balloon angioplasty. Stent delivery was successfully performed in all patients. One patient had thrombus formation in the stented vessel segment after implantation, and another was sent to bypass surgery because of persisting angina on the following day. No acute vessel closure was documented angiographically in 14 control patients after 24 hours. Long-term control angiograms after 4 to 6 months were recorded in 12 patients and showed vessel patency in 8, compared with 4 patients with late restenosis or reocclusion, of whom 3 had received multiple stent implantation.

ARRHYTHMIAS AND CONDUCTION DISTURBANCES

697**Reduction in the Frequency of Ventricular Late Potentials After Acute Myocardial Infarction by Early Thrombolytic Therapy**

Marc Zimmermann, Richard Adamec, and Stefano Ciaroni, with the technical assistance of Florida Malbois and Roland Tièche

To assess the effect of intravenous thrombolysis on the incidence of ventricular late potentials, 223 consecutive patients surviving a first acute myocardial infarction were included in the present study: 59 patients received intravenous recombinant tissue-type plasminogen activator (group A) and 164 patients (group B) received conventional medical treatment. A time-domain signal-averaged electrocardiogram and a high-resolution beat-to-beat recording were performed at 10 ± 3 days after infarction. The incidence of late potentials was 10% (6 of 59) in group A and 24% (39 of 164) in group B ($p < 0.05$). Among the 146 patients who underwent coronary arteriography, the incidence of late potentials was 13% (10 of 80) in patients with a patent infarct-related artery and 26% (17 of 66) in patients with an occluded infarct-related artery ($p < 0.05$). In conclusion, intravenous thrombolysis with recombinant tissue-type plasminogen activator reduces the incidence of late potentials in survivors of a first acute myocardial infarction and this reduced incidence appears to be related to the patency of the infarct-related artery.

Continued on page A26

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Sponsored by St. Luke's Medical Center and the William Dorros-Isadore Feuer Interventional Cardiovascular Disease Foundation, Ltd., Milwaukee



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1978

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Course Description and Objective —

This three day symposium on percutaneous interventional therapy of occlusive peripheral vascular disease will focus on the live demonstrations of peripheral angioplasty and atherectomy, and when indicated, adjunctive therapies.

The Sunday afternoon session focal point will be the diagnosis and management of occluded peripheral vascular disease patients and selected aspects of interventional procedures. Didactic sessions will include assessment of the ischemic limb, pertinent anatomy, ultrasound and other noninvasive imaging modalities, lytic therapy infusion, catheter and guidewire selection, and the technical aspects of arterial cannulation (including popliteal and contralateral techniques).

The subsequent two days will feature and emphasize live demonstrations of peripheral transluminal angioplasty (TA), atherectomy, and adjunctive devices, including stents, laser angioplasty, intraarterial ultrasound, angiography, and aspiration of a thromboembolus. In addition, peripheral vascular ultrasound imaging will be done in conjunction with the intervention in selected cases.

Interspersed between live interventional demonstrations will be edited video case presentations addressing specific topics. These cases will be introduced by a concise history and diagnostic arteriogram, and discussed by the faculty-panel and audience (group interaction to be facilitated by Instantaneous Reactive Interactive Systems [IRIS] who will on-line tally the audience's reaction). An edited video will then show how that particular case was managed. These cases will provide the learning environment for discussing the case selection process as well as the performance of particular interventional skills.

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Craig M. Walker, M.D.
Interventional Cardiology
and Medical Director
Cardiovascular Institute
of the South
Houma, Louisiana

Course Location — This symposium will be held at The Pfister Hotel in the floor Conference Center and will feature live video transmission from St. Luke's Medical Center bed private not-for-profit tertiary care cardiovascular medical center serving the southern area of Milwaukee County and surrounding communities.

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Course Outline —

Sunday, May 5	12:00 Noon	Registration/Exhibits Open
	1:00 PM - 5:00 PM	Didactic sessions
	5:00 PM - 6:30 PM	Complimentary Refreshments/View Exhibits
Monday, May 6	7:00 AM	Registration/Continental Breakfast/Exhibits Open
	8:00 AM - 5:30 PM	Demonstration Course
	6:30 PM - 10:30 PM	Cocktail Buffet and Entertainment at the Milwaukee Public Museum
Tuesday, May 7	7:00 AM	Continental Breakfast/Exhibits Open
	8:00 AM - 5:00 PM	Demonstration Course

Exhibits — Manufacturers of imaging equipment, angioplasty instrumentation, pharmaceuticals and cardiovascular interventional procedure materials will be represented. The exhibits will be open the following hours:

Sunday - May 5	12:00 Noon - 6:30 PM
Monday - May 6	7:00 AM - 5:30 PM
Tuesday - May 7	7:00 AM - 2:00 PM

Registration Fees — \$800 for MD/PhD (after April 10, fee will be \$850) \$400 for Residents, Fellows-In-Training, Nurses and Technicians (after April 10, fee will be \$450)

The registration fee includes all course materials, continental breakfasts, luncheons, refreshments cocktail buffet on May 6. (There is no additional charge for a spouse to attend the cocktail buffet.) **The for registration is April 10.**

Send Registration Form and check (drawn on US bank) payable to "Interventions 1991" to Judy Administrative Coordinator, 2901 W. Kinnickinnic River Parkway, Suite 403, Milwaukee, WI 532

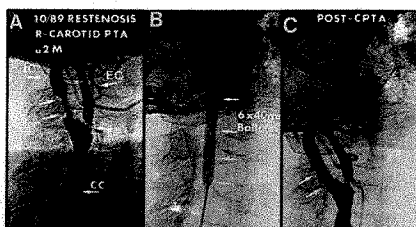
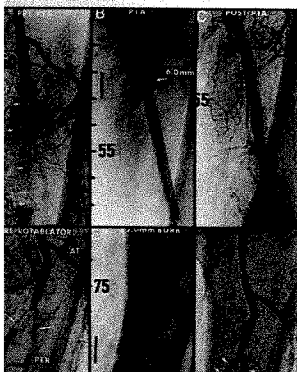
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For Further Information — To receive a complete brochure, please Judy Urfer at (414) 649-3594 or (800) 235-3594 or via FAX at (414) 649-8140.

St. Luke's Medical Center's diagnostic and interventional laboratories offer the most advanced imaging technology available, including Philips Digital Cardiac Imaging (DCI) system. DCI adds a new dimension of precision, speed of image processing, and high resolution imaging for cardiac and peripheral vascular studies. It differs from Digital Subtraction Angiography (DSA) because of the digital acquisition of imaging data, a technique in which the computer compensates for heart or body motion, and its capability of digital image enhancement which permits very fine pictorial detail. Pulsed fluoroscopy with a real-time edge enhancement algorithm produces remarkably high resolution video images for the peripheral as well as coronary arterial systems.

It's brighter, clearer images permit accurate diagnostic pictures which enable lesion treatment evaluation without waiting for processing of cine film. Real-time results are instantaneously available in the interventional procedure room for angioplasty, atherectomy, or laser procedure evaluation by comparison of before and after DCI images.

The DCI image display actually surpasses the quality of cine images and permits more accurate catheter placement, lesion assessment, ease of lesion crossing, and therapeutic procedural performance.



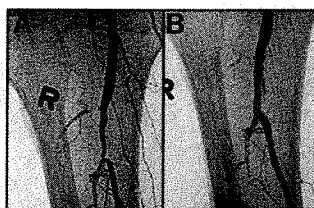
A Percutaneous transluminal angioplasty of a right internal carotid artery stenosis using a coaxial catheter technique.

▲ Percutaneous transluminal angioplasty of the superficial femoral and noniliac arteries. Tibiofemoral vessel

The benefits of DCI have been numerous and include:

- Diminution of fluoroscopic time, radiation dose to the physician and laboratory personnel, and overall procedural time.
- Immediate review of all runs on disk enables direct evaluation of all diagnostic information.
- Five (5) seconds of high contrast fluoroscopy allows for direct evaluation of specific sites even obese patients.
- Infrared remote control puts "freeze frame" road mapping under the direct control of the interv at tableside.
- Ease of use permits the physician to direct his full attention toward the procedural demands equipment.
- Automatic measurements can be obtained which include actual vessel dimensions and degree of can be used for procedural outcome and interventional assessment.
- Image acquisition rates of up to 60 frames per second.
- Image storage capacity of 16 road maps, 100 photo files and up to 24,000 disc images.
- Simultaneous cine and digital acquisition.
- Video and hard copy documentation for referring physicians.
- The DCI system additionally permits DSA as warranted in particular patient scenarios.

Successful lysis (Urokinase) and recanalization of the occluded left limb of an aorto-bifemoral graft without balloon angioplasty.



704

Late Outcome of Survivors of Out-of-Hospital Cardiac Arrest With Left Ventricular Ejection Fractions $\geq 50\%$ and Without Significant Coronary Arterial Narrowing

Peter J. Kudenchuk, Leonard A. Cobb, H. Leon Greene, Carol E. Fahrenbruch, and Florence H. Sheehan

Forty-three survivors of out-of-hospital ventricular fibrillation with minimal or no coronary artery stenoses and in whom left ventricular ejection fraction was ≥ 0.50 were evaluated. Of these patients, 30% had hypokinesia on left ventriculography, and 47% had a persistently abnormal electrocardiogram. Youth, and the presence of either wall motion or electrocardiographic abnormalities, defined patients with a several-fold higher risk of recurrent cardiac arrest compared with those without such characteristics. Although cardiac arrest is unusual in patients without major structural heart disease, its recurrence is more common in younger patients, and is also predicted by abnormalities detected on the electrocardiogram or by contrast left ventriculography.

709

Comparison of Clinical and Electrophysiologic Features of Preexcitation Syndromes in Patients Presenting Initially After Age 50 Years with Those Presenting at Younger Ages

Lynda E. Rosenfeld, Alice M. Van Zetta, and William P. Batsford

Of 73 patients with preexcitation documented by electrophysiologic studies, 13 (group 1) presented with their initial arrhythmias at an age > 50 years; 60 patients (group 2) were younger. All group 1 patients presented in the setting of acute or chronic diseases associated with middle age and often with atrial arrhythmias; only 13 group 2 patients had underlying illnesses ($p = 0.0001$). Wide complex tachycardia was more frequent in older patients (7 of 13 vs 11 of 60, $p < 0.05$). This, and the fact that the PR and QRS intervals of group 1 patients were within the normal range, differing significantly from those of group 2 patients (PR, 0.15 ± 0.04 vs 0.11 ± 0.03 second, $p < 0.001$; QRS, 0.09 ± 0.01 vs 0.12 ± 0.03 second, $p < 0.001$), made clinical and electrocardiographic identification of preexcitation more difficult. Concealed bypass tracts were more frequent in group 1 (5 of 13 vs 8 of 60, $p = 0.047$), but intraatrial conduction delays also contributed. Thus, specific age-related descriptors characterize patients > 50 years old who present with preexcitation syndromes. Awareness of these facts will enhance recognition of such patients.

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Usefulness of Flecainide for Prevention of Paroxysmal Atrial Fibrillation and Flutter

Adrian H. Pietersen and Henning Helleman, for the Danish Norwegian Flecainide Multicenter Study Group

To evaluate flecainide acetate in the prevention of paroxysmal atrial fibrillation and flutter, 43 patients were randomized blindly to either flecainide or placebo for 3 months in each period. Attacks were verified objectively by a minielectrocardiogram event recorder. All 43 patients were treated for ≥ 1 week in each period, 39 for ≥ 1 month, whereas 24 completed all 3 months in each period. In all 3 treatment intervals, there

Continued on page A32

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ETHMOZINE® (moricizine hydrochloride) TABLETS

INDICATIONS AND USAGE: ETHMOZINE is indicated for the treatment of documented ventricular arrhythmias, such as sustained ventricular tachycardia, that, in the judgement of the physician are life-threatening. Because of the proarrhythmic effects of ETHMOZINE, its use should be reserved for patients in whom, in the opinion of the physician, the benefits of treatment outweigh the risks. Initiation of ETHMOZINE treatment, as with other antiarrhythmic agents used to treat life-threatening arrhythmias, should be carried out in the hospital. Antiarrhythmic drugs have not been proven to improve survival in patients with ventricular arrhythmias. **CONTRAINDICATIONS:** ETHMOZINE is contraindicated in patients with preexisting second- or third-degree AV block and in patients with right bundle branch block when associated with left hemiblock (bifascicular block) unless a pacemaker is present. ETHMOZINE is also contraindicated in the presence of cardiogenic shock or known hypersensitivity to the drug. **WARNINGS:** **Mortality.** ETHMOZINE was one of three antiarrhythmic drugs included in the National Heart Lung and Blood Institute's Cardiac Arrhythmia Suppression Trial (CAST), a long-term multicenter, randomized, double-blind study in patients with asymptomatic non-life-threatening arrhythmias who had a myocardial infarction more than 6 days, but less than 2 years, previously. An excessive mortality or nonfatal cardiac arrest rate was seen in patients treated with both of the Class IC agents included in the trial, which led to discontinuation of those 2 arms of the trial. The ETHMOZINE and placebo arms of the trial are continuing. The applicability of the CAST results to other populations (e.g., those without recent myocardial infarction) and to agents other than IC (particularly to ETHMOZINE which, at this time remains in the trial) is uncertain. Considering the known proarrhythmic properties of ETHMOZINE and the lack of evidence of improved survival for any antiarrhythmic drug in patients without life-threatening arrhythmias, it is prudent to reserve the use of ETHMOZINE, as well as other antiarrhythmic agents, for patients with life-threatening ventricular arrhythmias. **Proarrhythmia.** Like other antiarrhythmic drugs, ETHMOZINE can provoke new rhythm disturbances or make existing arrhythmias worse. These proarrhythmic effects can range from an increase in the frequency of VPDs to the development of new or more severe ventricular tachycardia, e.g., tachycardia that is more sustained or more resistant to conversion to sinus rhythm, with potentially fatal consequences. It is often not possible to distinguish a proarrhythmic effect from the patient's underlying rhythm disorder, so that the occurrence rates given below must be considered approximations. Note also that drug-induced arrhythmias can generally be identified only when they occur early after starting the drug and when the rhythm can be identified, usually because the patient is being monitored. It is clear from the NIH-sponsored CAST (Cardiac Arrhythmia Suppression Trial) that some antiarrhythmic drugs can cause increased sudden death mortality, presumably due to new arrhythmias or asystole that do not appear early after treatment but that represent a sustained increased risk. Domestic premarketing trials included 1072 patients given ETHMOZINE; 397 had baseline lethal arrhythmias (sustained VT or VF and nonsustained VT with hemodynamic symptoms) and 576 had potentially lethal arrhythmias (increased VPDs or NSVT in patients with known structural heart disease, active ischemia, congestive heart failure or an LVEF < 40% and/or CI < 2.0 l/min/m²). In this population there were 40 (3.7%) identified proarrhythmic events, 26 (2.5%) of which were serious, either lethal (6), new hemodynamically significant sustained VT or VF (4), new sustained VT that was not hemodynamically significant (11) or sustained VT that became syncope/presyncope when it had not been before (5). In general, serious proarrhythmic effects were equally common in patients with more and less severe arrhythmias, 2.5% in the patients with baseline lethal arrhythmias vs. 2.8% in patients with potentially lethal arrhythmias, although the patients with serious effects were more likely to have a history of sustained VT (38% vs. 23%). Five of the six fatal proarrhythmic events were in patients with baseline lethal arrhythmias; four had prior cardiac arrests. Rates and severity of proarrhythmic events were similar in patients given 600–900 mg of ETHMOZINE per day and those given higher doses. Patients with proarrhythmic events were more likely than the overall population to have coronary artery disease (85% vs. 67%), history of acute myocardial infarction (75% vs. 53%), congestive heart failure (60% vs. 43%), and cardiomegaly (55% vs. 33%). All of the six proarrhythmic deaths were in patients with coronary artery disease; 5/6 each had documented acute myocardial infarction, congestive heart failure, and cardiomegaly. **Electrolyte Disturbances.** Hypokalemia, hypomagnesemia or hypomagnesemia may alter the effects of Class I antiarrhythmic drugs. Electrolyte imbalances should be corrected before administration of ETHMOZINE. **Sick Sinus Syndrome.** ETHMOZINE should be used only with extreme caution in patients with sick sinus syndrome, as it may cause sinus bradycardia, sinus pause or sinus arrest. **PRECAUTIONS: General.** **Electrocardiographic Changes/Conduction Abnormalities.** ETHMOZINE slows AV nodal and intraventricular conduction, producing dose-related increases in the PR and QRS intervals. In clinical trials, the average increase in the PR interval was 12% and the QRS interval was 14%. Although the QTc interval is increased, this is wholly because of QRS prolongation; the JT interval is shortened, indicating the absence of significant slowing of ventricular repolarization. The degree of lengthening of PR and QRS intervals does not predict efficacy. In controlled clinical trials and in open studies, the overall incidence of delayed ventricular conduction, including new bundle branch block pattern, was approximately 9.4%. In patients without baseline conduction abnormalities, the frequency of second-degree AV block was 0.2% and third-degree AV block did not occur. In patients with baseline conduction abnormalities, the frequencies of second-degree AV block and third-degree AV block were 0.9% and 1.4%, respectively. ETHMOZINE therapy was discontinued in 1.6% of patients due to electrocardiographic changes (0.6% due to sinus pause or asystole, 0.2% to AV block, 0.2% to junctional rhythm, 0.4% to intraventricular conduction delay, and 0.2% to wide QRS and/or PR interval). In patients with preexisting conduction abnormalities, ETHMOZINE therapy should be initiated cautiously. If second- or third-degree AV block occurs, ETHMOZINE therapy should be discontinued unless a ventricular pacemaker is in place. When changing the dose of ETHMOZINE or adding concomitant medications which may also affect cardiac conduction, patients should be monitored electrocardiographically. **Hepatic Impairment.** Patients with significant liver dysfunction have reduced plasma clearance and an increased half-life of ETHMOZINE. Although the precise relationship of ETHMOZINE levels to effect is not clear, patients with hepatic disease should be treated with lower doses and closely monitored for excessive pharmacologic effects, including effects on ECG intervals, before dosage adjustment. Patients with severe liver disease should be administered ETHMOZINE with particular care, if at all. **Renal Impairment.** Plasma levels of intact ETHMOZINE are unchanged in hemodialysis patients, but a significant portion (39%) of ETHMOZINE is metabolized and excreted in the urine. Although no identified active metabolite is known to increase in people with renal failure, metabolites of unrecognition importance could be affected. For this reason, ETHMOZINE should be administered cautiously in patients with impaired renal function. Patients with significant renal dysfunction should be started on lower doses and monitored for excessive pharmacologic effects, including ECG intervals, before dosage adjustment. **Congestive Heart Failure.** Most patients with congestive heart failure have tolerated the recommended ETHMOZINE daily doses without unusual toxicity or change in effect. Pharmacokinetic differences between ETHMOZINE patients with and without congestive heart failure were not apparent (see Hepatic Impairment above). In some cases, worsened heart failure has been attributed to ETHMOZINE. Patients with preexisting heart failure should be monitored carefully when ETHMOZINE is initiated. **Effects on Pacemaker Threshold.** The effect of ETHMOZINE on the sensing and pacing thresholds of artificial pacemakers has not been sufficiently studied. In such patients, pacing parameters must be monitored, if ETHMOZINE is used. **Drug Interactions.** No significant changes in serum digoxin levels or pharmacokinetics have been observed in patients or healthy subjects receiving concomitant ETHMOZINE therapy. Concomitant use was associated with additive prolongation of the PR interval, but not with a significant increase in the rate of second- or third-degree AV block. Concomitant administration of cimetidine resulted in a decrease in ETHMOZINE clearance of 49% and a 1.4 fold increase in plasma levels in healthy subjects. During clinical trials, no significant changes in the efficacy or tolerance of ETHMOZINE have been observed in patients receiving concomitant cimetidine therapy. Patients on cimetidine should have ETHMOZINE therapy initiated at relatively low doses, not more than 600 mg/day. Patients should be monitored when concomitant cimetidine therapy is instituted or discontinued or when the ETHMOZINE dose is changed. Concomitant administration of beta blocker therapy did not reveal significant changes in overall electrocardiographic intervals in patients. In one controlled study, ETHMOZINE and propranolol administered concomitantly produced a small additive increase in the PR interval. Theophylline clearance and plasma half-life were significantly affected by multiple dose ETHMOZINE administration when both conventional and sustained release theophylline were given to healthy subjects (clearance increased 44–66% and plasma half-life decreased 19–33%). Plasma theophylline levels should be monitored when concomitant ETHMOZINE is initiated or discontinued. Because of possible additive pharmacologic effects, caution is indicated when ETHMOZINE is used with any drug that affects cardiac electrophysiology. Uncontrolled experience in patients indicates no serious adverse interaction during the concomitant use of ETHMOZINE and diuretics, vasodilators, antihypertensive drugs, calcium channel blockers, beta blockers, ACE inhibitors, and warfarin. Plasma warfarin levels, warfarin pharmacokinetics, and prothrombin times were unaffected during multiple dose ETHMOZINE administration to healthy subjects. Results from *in vitro* studies do not suggest alterations in ETHMOZINE plasma protein binding in the presence of other highly plasma protein bound drugs. **CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY:** In a 24-month mouse study in which ETHMOZINE was administered in the feed at concentrations calculated to provide doses ranging up to 320 mg/kg/day, ovarian tubular adenomas and granulosa cell tumors were limited in occurrence to ETHMOZINE treated animals

indicate that both of these tumors are uncommon in the strain of mouse studied. In a 24-month study in which ETHMOZINE was administered by gavage to rats at doses of 25, 50 and 100 mg/kg/day, Zymbal's Gland Carcinoma observed in one mid-dose and two high-dose males. This tumor appears to be uncommon in the strain of rat studied. R of both sexes showed a dose-related increase in hepatocellular cholangiocarcinoma (also described as bile ductile cystadenoma or cystic hyperplasia) along with fatty metamorphosis, possibly due to disruption of hepatic choline utilization, phospholipid biosynthesis. The rat is known to be uniquely sensitive to alteration in choline metabolism. ETHMOZINE was not mutagenic when assayed for genotoxicity in *in vitro* bacterial (Ames test) and mammalian (Chinese hamster ovary hypoxanthine-guanine phosphoribosyl transferase and sister chromatid exchange) cell systems or in *in vivo* mammalian systems (rat bone cytogenetics and mouse micronucleus). A general reproduction and fertility study was conducted in rats at dose levels up to 6.7 times the maximum recommended human dose of 900 mg/day (based upon 50 kg human body weight) and revealed no evidence of impaired male or female fertility. **Pregnancy—Teratogenic Effects.** **Pregnancy Category B.** Teratology studies have been performed with ETHMOZINE in rats and in rabbits at doses up to 6.7 times the maximum recommended human daily dose, respectively, and have revealed no evidence of harm to the fetus. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, ETHMOZINE should be used during pregnancy only if clearly needed. **Pregnancy—Nonteratogenic Effects.** In a study in which rats were dosed with ETHMOZINE prior to mating, during mating and throughout gestation and lactation, dose levels 3.4 and 6.7 times the maximum recommended human dose produced a dose-related decrease in pup and maternal weight gain, possibly related to a larger litter size. In a study which dosing was begun on Day 15 of gestation, ETHMOZINE, at a level 6.7 times the maximum recommended human daily dose, produced a retardation in maternal weight gain but no effect on pup growth. **Nursing Mothers.** ETHMOZINE is secreted in the milk of laboratory animals and has been reported to be present in human milk. Because the potential for serious adverse reactions in nursing infants from ETHMOZINE, a decision should be made whether to discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use.** The safety and effectiveness of ETHMOZINE in children less than 18 years of age have not been established. **ADVERSE REACTION**

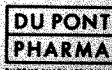
The most serious adverse reaction reported for ETHMOZINE is proarrhythmia (see WARNINGS). This occurred in 3.7% of 1072 patients with ventricular arrhythmias who received a wide range of doses under a variety of circumstances; addition to discontinuations because of proarrhythmias, in controlled clinical trials and in open studies, adverse reaction led to discontinuation of ETHMOZINE in 7% of 1105 patients with ventricular and supraventricular arrhythmias, including 3.2% due to nausea, 1.6% due to ECG abnormalities (principally conduction defects, sinus pause, junctional rhythm, AV block), 1% due to congestive heart failure, and 0.3–0.4% due to dizziness, anxiety, drug fever, urinary retention, blurred vision, gastrointestinal upset, rash, and laboratory abnormalities. The most frequently occurring adverse reactions in 1072 patients (including all adverse experiences whether or not considered ETHMOZINE-related by the investigator) were dizziness (15.1%), nausea (9.6%), headache (8.0%), fatigue (5.9%), palpitations (5.8%), and dyspnea (5.7%). Dizziness appears to be related to the size of each dose. In a comparison of 900 mg/day given at 450 mg b.i.d. or 300 mg t.i.d., more than 20% of patients experienced dizziness on the b.i.d. regimen vs. 12% on the t.i.d. regimen. Adverse reaction reported by less than 5%, but in 2% or greater of the patients were: sustained ventricular tachycardia, hypotension, abdominal pain, dyspnea, vomiting, sweating, cardiac chest pain, asthenia, nervousness, paresthesia, congestive heart failure, musculoskeletal pain, diarrhea, dry mouth, cardiac defect, sleep disorders, and blurred vision. Adverse reaction infrequently reported (in less than 2% of patients) were: Cardiovascular—hypotension, hypertension, syncope, supraventricular arrhythmias (including atrial fibrillation/flutter), cardiac arrest, bradycardia, pulmonary embolism, myocardial infarction, vasodilation, cerebrovascular events, thrombophlebitis; Nervous System—tremor, anxiety, depression, euphoria, confusion, somnolence, agitation, seizure, coma, abnormal gait, hallucinations, nystagmus, diplopia, speech disorder, ataxia, loss of memory, ataxia, abnormal coordination, dyskinesia, vertigo, linitis; Gastrointestinal—urinary retention or frequency, dysuria, urinary incontinence, kidney pain, impotence, decreased libido; Respiratory—hyperventilation, apnea, asthma, pharyngitis, cough, sinusitis; Gastrointestinal—anorexia, bitter taste, dysphagia, flatulence, ileus; Other—drug fever, hypothermia, temperature intolerance, eye pain, rash, pruritus, dry skin, urticaria, swelling of the lips and tongue, periorbital edema. During ETHMOZINE therapy, two patients developed thrombocytopenia that may have been drug-related. Clinically significant elevations in liver function tests (bilirubin, serum transaminases) and jaundice consistent with hepatitis were rarely reported. Although a cause and effect relationship has not been established, caution is advised in patients who develop unexplained signs of hepatic dysfunction, as consideration should be given to discontinuing therapy. Three patients developed rechallenge-confirmed drug fever; one patient experiencing an elevation above 103°F (to 105°F, with rigors). Fevers occurred at about 2 weeks in 2 cases and after 21 weeks in the third. Fevers resolved within 48 hours of discontinuation of moricizine. Adverse reactions were generally similar in patients over 65 (n=375) and under 65 (n=697), although discontinuation of therapy for reason other than proarrhythmia was more common in older patients (13.9% vs. 7.7%). Overall mortality was greater in older patients (9.3% vs. 3.9%), but those were not deaths attributed to treatment and the older patients had more serious underlying heart disease. The following table compares the most common (occurrence in more than 2% of the patient noncardiac adverse reactions (i.e., drug-related or of unknown relationship) in controlled clinical trials during the first or two weeks of therapy with ETHMOZINE, quinidine, placebo, disopyramide, or propranolol in patients with ventricular arrhythmias.

INCIDENCE (%) OF THE MOST COMMON ADVERSE REACTIONS
(THERAPY DURATION = 1-14 DAYS)

Adverse Reactions	>2% Moricizine No.	>2% Moricizine %	>2% Placebo No.	>2% Placebo %	>2% Quinidine No.	>2% Quinidine %	>5% Disopyramide No.	>5% Disopyramide %	>5% Propranolol No.	>5% Propranolol %
Total No. of Patients	1072		618		110		31		24	
Dizziness	121	11.3	33	5.3	8	7.3	-	-	2	8.3
Nausea	74	6.9	18	2.9	7	6.4	3	9.7	-	-
Headache	62	5.8	27	4.4	-	-	-	-	4	16.7
Pain	41	3.8	31	5.0	6	5.5	2	6.5	-	-
Dyspnea	41	3.8	22	3.6	-	-	-	-	-	-
Hypotension	40	3.7	-	-	3	2.7	-	-	-	-
Fatigue	33	3.1	16	2.6	6	5.5	2	6.5	3	12.5
Vomiting	22	2.1	-	-	-	-	-	-	-	-
Dry Mouth	-	-	-	-	-	-	11	35.5	-	-
Nervousness	-	-	-	-	-	-	3	9.7	-	-
Blurred Vision	-	-	-	-	3	2.7	2	6.5	3	12.5
Diarrhea	-	-	25	22.7	-	-	-	-	-	-
Constipation	-	-	-	-	-	-	2	6.5	-	-
Somnolence	-	-	-	-	-	-	-	-	2	8.3
Urinary Retention	-	-	-	-	-	-	4	12.9	-	-

OVERDOSAGE: Deaths have occurred after accidental or intentional overdoses of 2,250 and 10,000 mg of ETHMOZINE, respectively. **Signs, Symptoms and Laboratory Findings Associated with an Overdose of Drug.** Overdose with ETHMOZINE may produce emesis, lethargy, coma, syncope, hypotension, conduction disturbances, exacerbation of congestive heart failure, myocardial infarction, sinus arrest, arrhythmias (including junctional bradycardia, ventricular tachycardia, ventricular fibrillation and asystole), and respiratory failure. **Lethal Dose in Animals.** Oral doses of ETHMOZINE of about 200 mg/kg in dogs, 250 mg/kg in monkeys, 420 mg/kg in mice and 905 mg/kg in rats were lethal to about one-half of the animals exposed. Death was usually preceded by tremors, convulsions and respiratory depression. **Recommended General Treatment Procedures.** A specific antidote for ETHMOZINE has not been identified. In the event of overdose, treatment should be supportive. Patients should be hospitalized and monitored for cardiac, respiratory and CNS changes. Advanced life support systems, including an intracardiac pacing catheter, should be provided where necessary. Acute overdose should be treated with appropriate gastric evacuation, and with special care to avoid aspiration. Accidental introduction of ETHMOZINE into the lungs of monkeys resulted in rapid arrhythmic death.

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were significant reductions in the number of attacks ($p \leq 0.002$). Complete suppression with flecainide treatment was seen in 15 of 43 patients (35%) treated for 1 week, in 18 of 39 (46%) treated for 1 month and in 12 of 24 (50%) completing all 3 months. Adverse effects were reported in 32 of the 43 patients, with 2 withdrawals. One patient died suddenly. Thus, flecainide significantly suppresses the number of attacks of paroxysmal atrial fibrillation and flutter. Adverse effects were frequent but mostly tolerable.

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Time of Onset of Supraventricular Tachyarrhythmia in Relation to Alcohol Consumption

Markku Kupari and Pekka Koskinen

The etiology and the time of onset of supraventricular tachyarrhythmia was recorded in 289 patients aged <65 years who also underwent a screening test for alcoholism and an assessment of alcohol consumption during the week preceding the arrhythmia. Among 102 patients with idiopathic arrhythmias, patients with arrhythmias beginning on Saturdays or on Sundays were more often chronic, heavy drinkers (47%) than either patients with episodes beginning from Mondays through Fridays (22%) or control subjects from the out-of-hospital population (12%). The increased frequency of problem drinkers was mainly relative, however, and resulted from a decreased number of abstainers and non-problem drinkers. No conspicuous clustering of alcohol-related arrhythmias was seen after New Year's or May Day. These data support the role of alcohol in idiopathic weekend-onset arrhythmias but indicate that the question is of a relative rather than an absolute overrepresentation.

SYSTEMIC HYPERTENSION

723

Mean and Range of the Ambulatory Pressure in Normotensive Subjects from a Meta-Analysis of 23 Studies

Jan A. Staessen, Robert H. Fagard, Paul J. Lijnen, Lutgarde Thijs, Roger Van Hoof, and Antoon K. Amery

To perform a meta-analysis of published reports in an attempt to determine the mean and range of the normal ambulatory blood pressure (BP), 23 studies, including a total of 3,476 normal subjects, were reviewed. With weighting for the number of subjects included in the individual studies, the 24-hour BP averaged 118/72 mm Hg, the daytime BP 123/76 mm Hg and the nighttime BP 106/64 mm Hg. If the mean \pm 2 standard deviation intervals in the various studies were considered normal, the range of normality was 97 to 139/57 to 87 mm Hg for 24-hour BP, 101 to 146/61 to 91 mm Hg for daytime BP, and 86 to 127/48 to 79 mm Hg for nighttime BP.

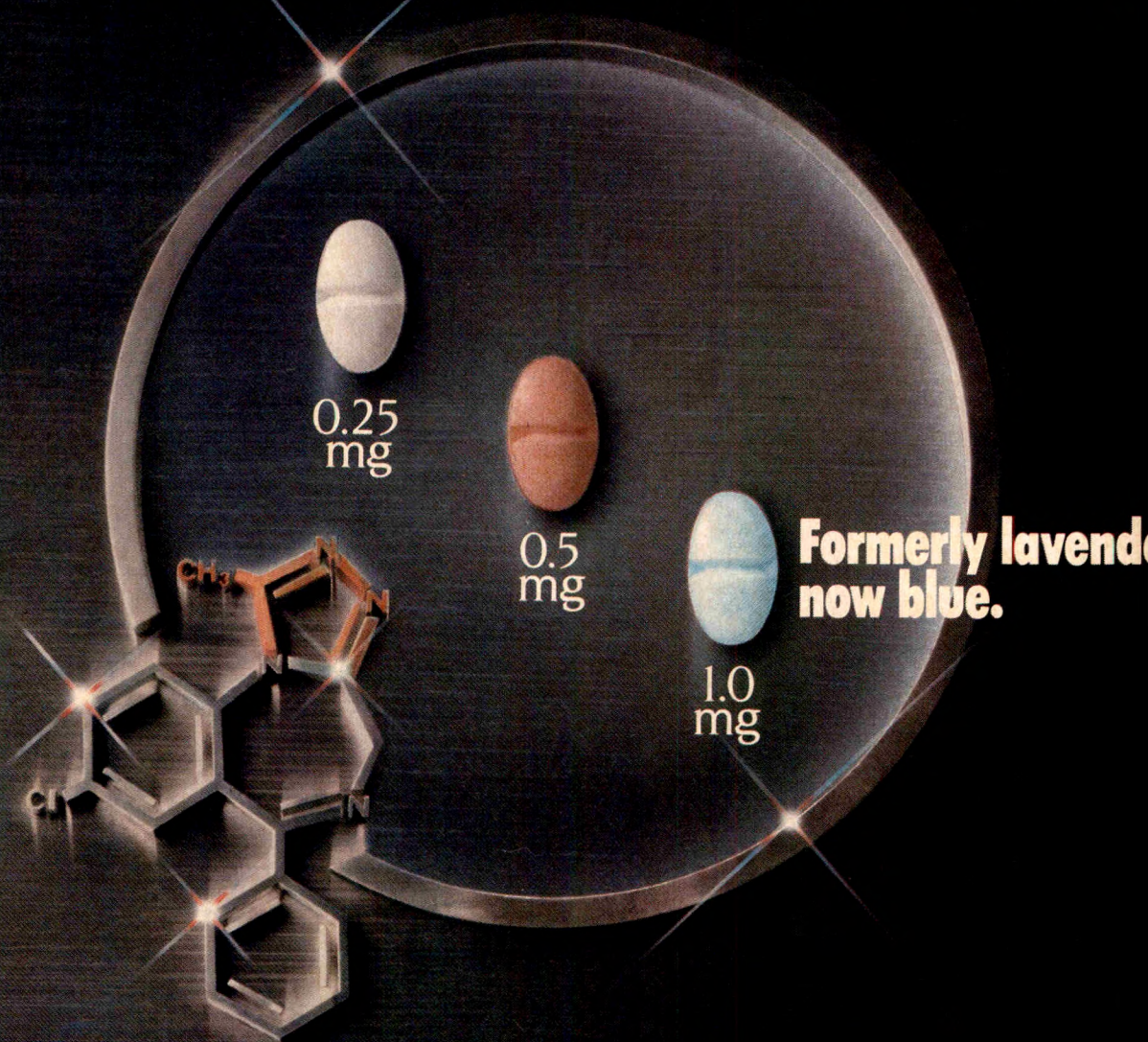
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Hemodynamic and Neurohormonal Effects of Quinidine in Patients with Severe Left Ventricular Dysfunction Secondary to Coronary Artery Disease or Idiopathic Dilated Cardiomyopathy

Stephen S. Gottlieb and Michelle Weinberg

Quinidine causes vasodilation and exerts negative inotropic activity. The consequences of these opposing actions have not been evaluated in patients with congestive heart failure. The hemodynamic and neurohormonal response to oral quinidine (600 mg) was therefore determined in 19 patients with severe chronic heart failure. Vasodilation was the predominant effect of quinidine, with reductions in mean arterial, left ventricular filling and right atrial pressures of 9, 8 and 15%, respectively. The quinidine-induced vasodilation increased plasma norepinephrine and epinephrine concentrations by 44 and 47%, respectively. No change in cardiac performance was noted, with the cardiac index slightly increased (10%) and stroke work index unchanged. Although the mean serum quinidine concentration was within the therapeutic range or lower in all patients, the quinidine concentration and the change in mean arterial pressure did correlate ($r^2 = 0.64$). In conclusion, vasodilation is the predominant hemodynamic effect of oral quinidine in patients with congestive heart failure.

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Effects of Prolonged Infusion of Human Alpha Calcitonin Gene-Related Peptide on Hemodynamics, Renal Blood Flow and Hormone Levels in Congestive Heart Failure

Y. Chandra Shekhar, Inder S. Anand, Raghav Sarma, Roberto Ferrari, Purshotam L. Wahi, and Philip A. Poole-Wilson

The effects of prolonged infusion of calcitonin gene-related peptide (CGRP) (8 ng/kg/min for 8 hours) on the hemodynamic functions, plasma hormones and renal blood flow were studied in 9 patients with congestive heart failure (New York Heart Association class III or IV, ejection fraction <35%). CGRP behaved like a balanced vasodilator. Systemic vascular resistance decreased more than pulmonary vascular resistance. There was no evidence of tachyphylaxis throughout the infusion. The hemodynamic effects were lost within 30 minutes of discontinuing CGRP. Renal blood flow and glomerular filtration rate increased. Plasma atrial natriuretic peptide decreased while cortisol increased. Other hormones remained unchanged. CGRP has sustained beneficial effects on hemodynamic indexes without adverse effects on hormones. Unlike many other vasodilators, CGRP also increases renal blood flow and glomerular filtration.

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CONGENITAL HEART DISEASE

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Analysis of Survival in Patients with Pulmonic Valve Atresia and Ventricular Septal Defect

Michael Hofbeck, Jan T. Sunnegårdh, Patricia E. Burrows, C. A. F. Moes, Nancy Lightfoot, William G. Williams, George A. Trusler, and Robert M. Freedom

This study reviews the clinical course of 104 consecutive patients with pulmonic valve atresia and ventricular septal defect who were diagnosed in the first year of life. Confluent pulmonary arteries supplied by a single ductus were present in 72 patients (69%, group I), whereas 32 patients (31%, group II) had a pulmonary blood supply partially or exclusively dependent on systemic collateral arteries. An estimate of the probability of survival for 10 years was 69% in both groups. Corrective surgery was performed in 33 of 72 group I patients (46%) versus 5 of 32 group II patients (16%). Arborization abnormalities and intrapulmonary stenoses accounted for the lower probability of undergoing corrective surgery in group II patients.

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Pulmonary Artery Morphology and Hemodynamics in Pulmonic Valve Atresia with Ventricular Septal Defect Before and After Repair

Yasuhisa Shimazaki, Masahiko Iio, Susumu Nakano, Shizuo Morimoto, Seiichiro Ikawa, Hikaru Matsuda, and Yasunaru Kawashima

Cardiac catheterization and angiographic studies were performed in 22 patients with pulmonic valve atresia and ventricular septal defect before and after repair. Mean postoperative pulmonary artery pressure (PAP) ranged from 9 to 92 mm Hg (mean 28 ± 19) and pulmonary vascular resistance ranged from 1.1 to 35.2 $\text{U} \cdot \text{m}^2$ (mean 6.4 ± 8.0), and these data correlated. The number of (effective) pulmonary artery subsegments connected to the central pulmonary arteries ranged from 22 to 42 (mean 38 ± 6). Pulmonary vascular resistance correlated with the number of effective subsegments ($r = -0.85$, $p < 0.001$), the mean preoperative PAP ($r = 0.79$, $p < 0.001$), the sum of the pulmonary artery areas after branching ($r = -0.73$, $p < 0.001$) and the postoperative pulmonary artery area index of the right and left pulmonary arteries at prebranching ($r = 0.70$, $p < 0.001$). The incidence of pulmonary vascular resistance being $< 3.0 \text{ U} \cdot \text{m}^2$ was higher in patients with > 36 effective subsegments and with a preoperative pulmonary artery area index > 0.5 ($p < 0.01$). Postoperative PAP and pulmonary vascular resistance may be predictable when the pulmonary artery area and the number of effective subsegments are measured before repair. Early palliation to increase pulmonary artery size and the number of effective subsegments is recommended for obtaining normal pulmonary hemodynamics after repair.

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MISCELLANEOUS

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Catheter-Based Intravascular Ultrasound Imaging of Chronic Thromboembolic Pulmonary Disease

François Ricou, Pascal H. Nicod, Kenneth M. Moser, and Kirk L. Peterson

Pulmonary thromboendarterectomy is the treatment of choice for pulmonary hypertension due to chronic pulmonary thromboemboli. A precise assessment of location and extension of these thrombi is important as only proximal chronic pulmonary thromboemboli are accessible to surgery. Because intravascular ultrasound imaging can assess not only arterial luminal size, but also wall thickness, its value as a complement to angiography was assessed in 11 patients with severe pulmonary hypertension. Results show that intravascular ultrasound of pulmonary arteries is feasible and safe in patients with pulmonary hypertension. It may help to assess the location and the extent of the pathologic process involving pulmonary arteries.

METHODS

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Assessment of Right Ventricular Oxidative Metabolism by Positron Emission Tomography with C-11 Acetate in Aortic Valve Disease

Rodney J. Hicks, Victor Kalff, Vicky Savas, Mark R. Starling, and Markus Schwaiger

Evaluation of right ventricular (RV) oxidative metabolism is limited by the inability to determine oxygen extraction by the right ventricle and its complex morphology. The feasibility of positron emission tomography-derived RV C-11 acetate clearance kinetics for evaluation of RV oxidative metabolism was assessed in 21 patients with noncoronary cardiac disease. RV C-11 clearance rate constants correlated significantly with RV hemodynamic data ($r = 0.7$, $p < 0.05$). Patients were stratified into subgroups with normal and elevated pulmonary pressures, and compared with 10 normal control subjects. RV C-11 clearance rate constants were significantly higher in the subgroup with elevated ($n = 13$) pulmonary artery pressures than in patients with normal ($n = 8$) pulmonary artery pressures, and in normal control subjects ($p < 0.05$). These preliminary data suggest that RV C-11 acetate clearance rate constants can provide noninvasive evaluation of RV oxidative metabolism.

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Validity of Catheter-Tip Doppler Technique in Assessment of Coronary Flow Velocity and Application of Spectrum Analysis Method

Masakazu Yamagishi, Daisuke Hotta, Jun Tamai, Satoshi Nakatani, and Kunio Miyatake

To determine absolute coronary flow velocity, flow velocity was measured using a Doppler catheter in which signals were analyzed by a custom-

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*CAPOTEN (captopril tablets) is indicated in patients with heart failure who have not responded adequately to treatment with diuretics and digitalis. Although the beneficial effect of captopril in heart failure does not require the presence of digitalis, most controlled clinical trial experience with captopril has been in patients receiving digitalis, as well as diuretic treatment. Consequently, CAPOTEN should generally be added to both of these agents except when digitalis use is poorly tolerated or otherwise not feasible. In using CAPOTEN, consideration should be given to the risk of neutropenia/agranulocytosis. Use special precautions in patients with impaired renal function, collagen vascular disorders, or those exposed to other drugs known to affect the white blood cells or immune response. Evaluation of heart failure patients should always include assessment of renal function. Please see INDICATIONS AND USAGE, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS in the

designed fast-Fourier transformation analysis system. In the in vitro model, the measured flow velocity was well correlated with actual flow velocity ($y = 1.01x + 1.5$, $r = 0.988$). In clinical cases, flow velocity pattern in the left anterior descending artery was shown to have predominant diastolic components that were preceded by small systolic components. The peak flow velocity of diastolic components was 44 ± 12 cm/s (mean \pm standard deviation) and that of systolic components 17 ± 8 cm/s. During rapid atrial pacing, an increase in flow velocity was well correlated with an increase in great cardiac vein flow. It is suggested that the Doppler catheter technique with full spectrum analysis is useful in clinically assessing coronary flow velocity pattern.

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Comparison of Celiprolol and Propranolol in Stable Angina Pectoris

William H. Frishman, MD, Mark Heiman, MD, Judith Soberman, MD,
Steven Greenberg, MD, and Jack Eff, MD,
for the Celiprolol International Angina Study Group*

The comparative antianginal effects and safety of propranolol and celiprolol, a highly β_1 -selective adrenoceptor blocker with selective partial β_2 -adrenoceptor agonist activity, were assessed in an international multicenter, placebo run-in, active control, double-blind, randomized, titration-to-effect study of 140 patients with stable, exercise-induced angina pectoris. At baseline, all patients received placebo for 2 weeks, then titrated doses of once-daily celiprolol (200, 400, 600 mg) or twice-daily propranolol (total daily dose 80, 160, 320 mg) over 4 weeks, followed by a 2-week maintenance period. Heart rate and blood pressure, at rest and with exercise, weekly anginal attack frequency, nitroglycerin consumption and symptom-limited treadmill exercise times (modified Bruce protocol) were assessed. Compared with their respective baselines, both celiprolol and propranolol reduced anginal attack and nitroglycerin consumption rates to a comparable degree, while improving exercise tolerance ($p < 0.05$). Treatment with propranolol compared with celiprolol, however, was associated with a significantly lower heart rate at rest ($p < 0.01$). The double-product at the conclusion of exercise testing was significantly reduced by both drugs. Celiprolol and propranolol had similar effects on blood pressure, and were well tolerated. More symptomatic bradycardia occurred with propranolol. Despite the differences in their hemodynamic actions, once-daily celiprolol is as effective as twice-daily propranolol in the treatment of patients with stable angina pectoris.

(Am J Cardiol 1991;67:665-670)

From the Department of Medicine, The Albert Einstein College of Medicine, Bronx, New York. This study was sponsored in part by Rhône-Poulenc Rorer, Horsham, Pennsylvania. Manuscript received October 5, 1990; revised manuscript received and accepted November 26, 1990.

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*See Appendix.

Beta-adrenergic blocking drugs are widely accepted in the treatment of patients with angina pectoris.^{1,2} Celiprolol is a relatively long-acting β_1 -selective adrenergic blocker with selective β_2 -adrenergic agonist activity.³ Unlike classic β blockers, celiprolol appears not to depress cardiac contractility at rest, and causes systemic vasodilation, its major mechanism for reducing blood pressure at rest.⁴ The drug has been shown to be effective in the treatment of patients with systemic hypertension,^{5,6} and those with arrhythmia.⁷ To assess the potential advantages of a selective β_1 blocker with vasodilating activity, this study was designed to identify differences, if any, in the antianginal effectiveness and safety of celiprolol versus propranolol in patients with chronic stable angina pectoris.

To decrease the variability of treadmill exercise stress test results, the entry requirements included a window of 3 to 7.5 minutes in which all qualifying patients experienced exercise-limiting angina during 2 tests before randomization, a requirement that had not yet become common for entry into antianginal clinical studies when this study was started.

METHODS

Patient population: One hundred forty men and women aged 21 to 80 with a primary diagnosis of chronic, stable, exertional angina for ≥ 3 months before enrollment were considered for entry. Patients were to have a cardiac status characterized as uncompromised, slightly compromised, or moderately compromised (Canadian Heart Association class I or II).

Patients were excluded if they had myocardial infarction, coronary artery bypass surgery, angioplasty within 4 months, chest pain at rest or unstable angina, congestive heart failure, poor myocardial contractility, significant valvular disease, sinus bradycardia or heart block $>1^\circ$, arrhythmia requiring concomitant therapy; supine diastolic blood pressure >104 mm Hg; supine systolic blood pressure >180 mm Hg or hypertension requiring concomitant medications other than diuretics or up to 1,000 mg/day of alpha-methyldopa, or both; chronic obstructive lung disease requiring concomitant therapy; and insulin-requiring or uncontrolled diabetes mellitus.

Patients were enrolled in 13 centers located in South America, the United States, and Europe, and signed an approved informed consent form.

Study design (Figure 1): Qualifying patients were enrolled in this multicenter, double-blind, parallel, randomized trial to compare the safety and efficacy of celiprolol at titrated doses of 200, 400 and 600 mg/day with propranolol at titrated doses of 40, 80 and 160 mg twice/day for the treatment of chronic exertional angina pectoris.

At the initial visit, ≥ 1 treadmill exercise tolerance test was performed to determine the starting stage of the modified Bruce protocol that would consistently result in termination due to exercise-limiting angina lasting between 3 to 7.5 minutes of total exercise. In addition to the angina, each qualifying exercise electrocardiogram was required to reveal a horizontal or downsloping ST-segment depression lasting ≥ 1.0 minute, measured 0.08 second after the J point, within 2 minutes after termination of exercise.

After the appropriate starting stage was established, 2 more exercise stress tests meeting the aforementioned criteria qualified patients for double-blind treatment after ≥ 2 weeks of placebo lead-in. The second test had to be performed on the qualifying day, but the first could be performed at a time not < 15 hours or > 9 days before the second test.

At each of the 2 weekly visits before double-blind treatment, 0.4 mg of sublingual nitroglycerin and a sufficient quantity of twice-daily placebo medication externally identical in appearance to the active medication was dispensed.

Patients who met the specific entry criteria were randomly allocated to celiprolol or propranolol treatment groups by a computer-generated code. During the first 2 weeks of active treatment, patients received either 200 mg/day of celiprolol in the morning and placebo in the evening, or 40 mg of propranolol twice/day. At the end of these first 2 weeks, patients underwent repeat exercise testing. Those who did not have an increase of $\geq 20\%$ over baseline in the time to exercise-limiting angina were titrated to either 400 mg of celiprolol once each morning or to 80 mg of propranolol twice/day. At the end of the next 2 weeks, patients again underwent exercise testing. Patients who did not

achieve an improvement $\geq 20\%$ in exercise time were titrated to the next higher dose of either celiprolol (400 or 600 mg once each morning) or to propranolol (80 or 160 mg twice/day), which they took for 2 weeks before returning for the final double-blind treadmill evaluation. The active treatment phase was followed by a 1-week down-titration (tapering) and a subsequent 1-week single-blind placebo lead-out phase.

Methods of observation: All patients kept a detailed daily diary of anginal episodes and the amount of sublingual nitroglycerin consumed to abort anginal attacks. Diaries were analyzed at each visit to determine weekly episodes of angina and sublingual nitroglycerin consumption. Diary accuracy was confirmed by counting nitroglycerin tablets. Likewise, compliance was assessed by counting the study drug pill at each visit.

At study entry (or during placebo lead-in) all patients underwent a complete history and physical examination, and a fasting clinical laboratory evaluation comprising a complete blood count, a urinalysis and biochemical screen, a chest x-ray (optional), and a 12-lead electrocardiogram. An optional ophthalmologic examination was performed. These procedures were repeated either at the end of the down-titration or placebo lead-out phases.

Patients were seen for 2 visits during the single-blind placebo phase (or for 1 visit only if both qualifying exercise tests were performed after the 2-week placebo lead-in), for every 2 weeks during the double-blind titration phase, and again after 1 week of the down-titration and placebo lead-out phases. At each visit, supine pulse rate and blood pressure were recorded, and a brief cardiovascular examination was performed and 12-lead electrocardiogram obtained.

Data on adverse experiences were compiled from patient reports (undirected history) and from direct observations made by the investigator. Adverse clinical and laboratory experiences were evaluated by the investigator for severity, clinical significance, and relation to drug administration.

Exercise testing: Multistage treadmill exercise testing was performed according to a modification of the Bruce protocol⁸ during the first through the sixth visits and at the eighth visit. The appropriate starting stage at which to achieve exercise-limiting angina in 3 to 7.5

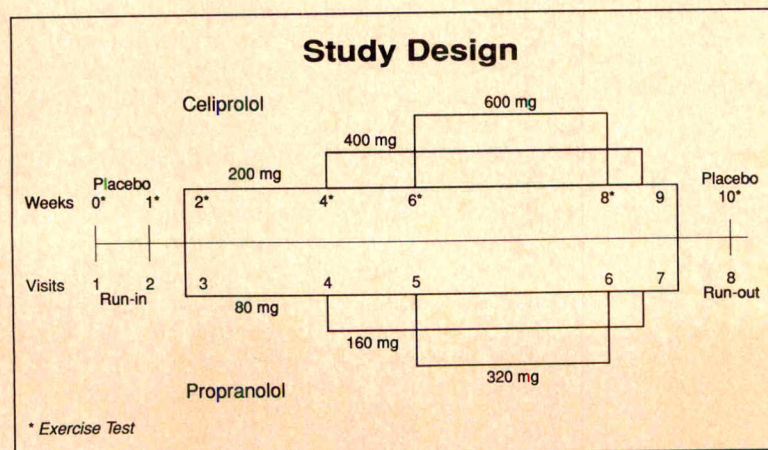


FIGURE 1. Study protocol.

minutes was determined at the first visit. All subsequent exercise tests were to begin at this stage. The final exercise test performed during the single-blind placebo phase was used as baseline for purposes of comparison. Exercise tests were performed from 20 to 28 hours after the previous morning dose and from 10 to 14 hours after the previous evening dose.

Heart rate and blood pressure were measured every 3 minutes during exercise, at the onset of angina, at the onset of 1-mm ST depression, at the onset of exercise-limiting angina, at the termination of exercise (if different from all of the above), and at a minimum of 1 and 2 minutes into recovery. Continuous electrocardiographic monitoring was used and sample recordings obtained every minute during exercise and recovery, and at the time of onset of angina, 1-mm ST depression, exercise-limiting angina or exercise termination. Times (in minutes and seconds) to the onset of angina, 1-mm ST depression and exercise-limiting angina or exercise termination were recorded.

During the active treatment phase, before exercise-limiting angina, the protocol required termination of treadmill testing if any of the following occurred: >90% maximal predicted heart rate, supraventricular tachycardia, premature ventricular contractions >25%, ventricular tachycardia, intracardiac block precipitated by exercise, peripheral circulatory insufficiency; either an acute decrease in systolic blood pressure or a failure of systolic blood pressure to increase >10 mm Hg; systolic blood pressure >260 mm Hg, diastolic blood pressure >120 mm Hg, ≥ 3 -mm ST depression, excessive dyspnea or fatigue, failure to increase heart rate after 6 minutes of exercise, ataxic gait, or at the patient's request.

Statistical methods: Data presented are mean \pm standard deviation. Baseline data were compared using a 2-way analysis of variance, except for sex and race—variables that were compared with a chi-square test, with $p < 0.05$ chosen as the level of statistical significance. Comparisons between baseline and end-of-treatment data, and between celiprolol- and propranolol-treated groups, were included, using analysis of variance based on 2-tailed t tests, with $p < 0.05$ chosen as the level of statistical significance.

Materials: All materials, including study medications, were provided by the sponsor, Revlon Health Care Corporation, Tuckahoe, New York, which is now Rhône-Poulenc Rorer, Inc., Fort Washington, Pennsylvania.

RESULTS

One hundred nine men and 31 women ($n = 140$) were randomized to receive double-blind active treatment; 67 were assigned to celiprolol once a day and 73 to propranolol twice a day. Baseline demographic and exercise characteristics are listed in Table I. There were no significant differences between groups for any of the demographic and baseline variables ($p > 0.05$).

Before the study was unblinded, 21 of 67 celiprolol- and 30 of 73 propranolol-treated patients were identified for the protocol-evaluable population. Most protocol violations resulted from inappropriate timing of

TABLE I Baseline Characteristics (Mean \pm SE)

	Celiprolol ($n = 67$)	Propranolol ($n = 73$)	p Value
Male (%)	79	77	0.73
Age (yr)	60.3 \pm 1.0	60.5 \pm 1.1	0.64
Weight (kg)	75.2 \pm 1.5	76.7 \pm 1.3	0.50
Race (% white)	91	93	0.64
Time to exercise-limiting angina (min)	5.79 \pm 0.17	5.86 \pm 0.16	0.79
Time to 1-mm ST-depression (min)	3.99 \pm 0.22	3.99 \pm 0.21	0.92
Time to onset of angina (min)	4.10 \pm 0.16	4.10 \pm 0.15	0.95
SE = standard error.			

treadmill tests relative to drug administration, and inappropriate titration of dose based on treadmill test response; as a result, the protocol-evaluable population completing the double-blind active treatment phase and used in the analysis comprised 17, 17 and 12 patients ($n = 46$) who were appropriately maintained at 200, 400 and 600 mg/day of celiprolol, respectively, and 21, 7 and 15 patients ($n = 43$) maintained at 40, 80 and 160 mg twice/day of propranolol, respectively.

The efficacy of propranolol and celiprolol for the treatment of chronic stable exertional angina was assessed by patient diaries (for anginal attack frequency and nitroglycerin consumption) and exercise treadmill test data after 6 weeks of active treatment (sixth visit). The primary treadmill variables used to assess efficacy were the times to the onsets of angina, 1-mm ST depression, and exercise-limiting angina. When none of these end points occurred, total exercise time was used in their stead. Secondary efficacy parameters were double-products at peak exercise and at maximal attained work load. Comparisons between the celiprolol and propranolol groups are summarized in Table II. There were no significant differences between treatment groups for any of the end points analyzed. There was a near-significant difference in the change from baseline for double-product at maximal workload. The decrease in heart rate at rest was significantly greater for the propranolol group than for the celiprolol group. Both groups had significant improvements over baseline treadmill testing for times to the onsets of exercise-limiting angina, angina, 1-mm ST depression, and patient diary evaluations of weekly anginal attack rate. The double-product at peak exercise also decreased significantly in both groups. Weekly nitroglycerin consumption significantly decreased in the propranolol but not in the celiprolol group. There was no significant difference between celiprolol and propranolol based on the number of patients categorized as responders ($\geq 20\%$ improvement in total exercise time compared with baseline, 59 vs 47%, respectively, $p = 0.22$).

Additional analysis was performed for all patients randomized to double-blind active treatment, except for 2 celiprolol patients and 1 propranolol patient who were excluded because they did not undergo treadmill tests while in the active treatment phase. In terms of the last treadmill test performed, there was no difference between treatment groups for times to exercise-limiting angina, 1-mm ST depression or onset of angina.

Safety: All 140 patients randomized to active treatment were included in the safety evaluation. The total number of patients (n = 24) reporting adverse experiences was similar for both groups (celiprolol 12 [34%], propranolol 12 [30%]). Likewise, reactions deemed pos-

sibly or definitely related to the study drug by the investigators before unblinding occurred in a similar percentage for both the celiprolol and propranolol groups (18 and 16%, respectively), although the 7 patients with the 11 adverse experiences considered definitely related

TABLE II Comparison of Changes from Baseline for Celiprolol and Propranolol Treatment Groups (Mean \pm SD)

	Celiprolol (mean dose 378 mg q.d.)		Propranolol (mean dose 78.6 mg b.i.d.)		p Value— C vs P
	Baseline	Change from Baseline	Baseline	Change from Baseline	
	Protocol-Evaluable Population				
	(n = 46)		(n = 43)		
Time to exercise-limiting angina (min)	5.67	1.39 ± 1.39*	5.79	1.54 ± 1.72*	0.96
Time to 1-mm ST depression (min)	4.16	1.68 ± 1.67*	3.94	1.28 ± 1.58*	0.27
Time to onset of angina (min)	3.93	1.66 ± 1.70*	4.04	1.88 ± 2.07*	0.90
Double-product at maximal exercise (beats/min · mm Hg × 10 ²)	223.9	-37.2 ± 39.5*	227.0	-49.9 ± 42.9*	0.09
Resting heart rate (beats/min)	72.4	-2.83 ± 7.65	71.7	-12.7 ± 7.67*	<0.01
All Patients with Evaluable Diary Data					
Weekly angina attack rate	(n = 59) 5.5	-2.7 ± 4.7*	(n = 55) 3.4	-2.1 ± 2.8*	0.51
Weekly nitroglycerin consumption	(n = 56) 2.0	-0.4 ± 2.4	(n = 51) 1.9	-1.3 ± 3.2*	0.15

* p <0.05 for difference from baseline means.

* p < 0.05 for difference from baseline means.

TABLE III Adverse Clinical Experiences

Body System	Celiprolol		Propranolol	
	No. Reported*	No. Related†	No. Reported*	No. Related†
Cardiovascular	3	3	5	4
(bradycardia)	(0)	(0)	(4)	(4)
(other)	(3)	(3)	(1)	(0)
Eye, ear, nose, throat	2	1	0	0
Gastrointestinal	8	5	8	2
(abdominal pain)	(3)	(3)	(3)	(0)
(other)	(5)	(2)	(5)	(2)
Genitourinary	1	0	1	1
Musculoskeletal	11	6	1	0
(pain/cramps)	(9)	(5)	(1)	(0)
(other)	(2)	(1)	(0)	(0)
Nervous	7	6	6	6
(headache)	(2)	(2)	(2)	(2)
(dizzy/faint)	(2)	(1)	(3)	(3)
(other)	(3)	(3)	(1)	(1)
Psychiatric	1	1	0	0
Respiratory	5	1	6	6
Other	4	4	8	7
(death)	(0)	(0)	(1)	(0)
(fatigue)	(4)	(4)	(7)	(7)
Total	42	27	35	26

* Some patients reported >1 adverse experience.

† Relation to study drug determined by investigators before unblinding.

were all in the propranolol group. The most frequently reported adverse reactions were tiredness/fatigue (celiprolol 4 [6%], propranolol 7 [10%]), leg cramps (celiprolol 3 [4%] and propranolol 0 [0%]) and symptomatic bradycardia (celiprolol 0 [0%] and propranolol 4 [6%]). Electrocardiographic changes from baseline, consistent with sinus bradycardia, were noted in 59% of the propranolol patients but in only 21% of the celiprolol patients. Data relating to adverse experiences are summarized in Table III.

DISCUSSION

Beta-adrenergic blockers have gained wide acceptance for the treatment of patients with stable and unstable angina pectoris when used alone or in combination with other antianginal therapies.¹ Their antianginal and antiischemic effectiveness relates to their ability to decrease heart rate, blood pressure and myocardial contractility at rest, while attenuating increments in both heart rate and blood pressure during exercise.⁹ Although coronary artery resistance may not change or may even increase with many β blockers, total coronary blood flow may still be maintained by the increase in diastolic coronary perfusion time observed with lower heart rates.⁹

More controversial is the relative antianginal effectiveness of β blockers with partial agonist activity.^{10,11} Heart rate reduction is a major contributor to the antianginal effects of β blockers, and because agents with partial agonism have minimal bradycardic action, it has been suspected that they might be less effective as treatments for angina.

Celiprolol is a unique drug with selective β_1 -adrenergic blocking activity and selective partial β_2 -adrenergic agonism. Unlike the β blockers propranolol and metoprolol, celiprolol has been shown to be a peripheral vasodilator, and causes less reduction in cardiac output and heart rate at rest.^{4,12} It is a long-acting drug that can be used once a day in the treatment of hypertension.^{5,13,14}

To ensure reproducibility and consistency of data in this study, we used a relatively narrow window of time to exercise-limiting angina (3 to 7.5 minutes) at baseline, which appeared to reduce variability in the results. This study demonstrated that once-daily celiprolol has comparable effects to therapeutic doses of propranolol in the treatment of patients with angina pectoris regarding the improvement of exercise tolerance time on the treadmill and the relief of anginal symptoms. Exercise time to 1-mm ST-segment depression was prolonged equally with both drugs. Propranolol was associated with a lower heart rate at rest than celiprolol. The rate-pressure product was significantly reduced by both drugs. Propranolol and celiprolol had similar effects on blood pressure.

Celiprolol and propranolol were well tolerated in the study, with fewer episodes of severe bradycardia with celiprolol.

Although its hemodynamic activity is different from that of propranolol, celiprolol in doses of 200 to 600

mg/day is a safe and effective drug treatment for angina pectoris. The vasodilator activity of celiprolol could cause a lesser end-diastolic volume increment than is seen with the more bradycardic agent propranolol. This effect of celiprolol would tend to cause a lesser increase in wall tension and myocardial oxygen consumption, which could offset its lesser bradycardic action. Further studies of celiprolol's effects on coronary vasculature may better elucidate any possible advantages of celiprolol over propranolol and other β blockers without β_2 -agonist activity.

Partial β_2 -adrenergic receptor agonism does not interfere with the therapeutic effectiveness of a β blocker used for the treatment of angina pectoris. This property in a β blocker may also provide a margin of safety for patients with unacceptably low heart rates while receiving propranolol, and for patients with left ventricular dysfunction. The role of celiprolol in reducing the risk of morbidity and mortality in patients with myocardial infarction remains to be determined.

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APPENDIX

Participating Investigators

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Effects of Atenolol Alone, Nifedipine Alone and Their Combination on Ambulant Myocardial Ischemia

James A. Hill, MD, Jose I. Gonzalez, MD, Robert Kolb, RN, and Carl J. Pepine, MD

The effects of atenolol (100 mg/day) and nifedipine (20 mg 3 times daily) and their combination on ambulant myocardial ischemia were investigated using a randomized, double-blind, placebo-controlled, crossover trial. Eighteen men with symptomatic coronary artery disease, exercise-induced ischemia and minimal symptoms, underwent 4 blinded treatment periods of 2 weeks' duration (2 placebo, 1 atenolol, 1 nifedipine). Those that did not have ischemia eliminated by monotherapy received combination therapy with both drugs. Forty-eight-hour ambulatory electrocardiographic monitoring was used to quantitate ischemic parameters at the end of each period. Both nifedipine and atenolol as monotherapy reduced the number of ischemic episodes and the average duration of each episode compared with placebo ($p < 0.05$). Compared with placebo, nifedipine reduced the total duration of ischemia ($p < 0.05$) but the effect of atenolol on ischemia duration was of borderline significance ($p = 0.066$). There were no differences in reduction of ischemic parameters when atenolol was compared with nifedipine (difference not significant). In the 9 patients who continued to have ischemia with monotherapy, combination therapy eliminated it in 2 and reduced the duration by $>50\%$ in the remaining patients compared with placebo. In conclusion, monotherapy with nifedipine or atenolol is similarly effective in eliminating or reducing ambulant ischemia. Combination therapy can provide additional benefit in those with continued ischemia.

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Evaluation of myocardial ischemia has traditionally been based on determining the threshold of myocardial oxygen demand that causes demonstrable ischemia manifest as angina pectoris. Ambulatory electrocardiographic monitoring has enabled the identification of episodes of myocardial ischemia that are frequently not associated with chest pain or its equivalents and often occur at indexes of myocardial oxygen demand much lower than those achieved by the same patient during exercise testing. Recent data suggest that when antianginal agents are given to provide what appears to be good symptom control, a substantial number of patients continue to have ambulant ischemia,^{1,2} which has been associated with an adverse outcome.³

These findings raise questions about medical therapy and its ability to prevent not only symptoms but also ischemia, and how antiischemic therapy should be used and monitored. We⁴ previously reported data using dose titration of the β -blocking agent metoprolol in minimally symptomatic patients with modification of ambulant ischemia as the end point of therapy. The purpose of the current study was to extend our observations on the modification of ischemia in minimally symptomatic patients based on ischemia and not on symptoms. Because ambulant ischemia appears to occur by a mechanism not simply related to myocardial oxygen demand, it seems appropriate to examine the effects of medications that have potentially different actions on preventing ischemia. Accordingly, the effects of atenolol and nifedipine, alone and in combination, on ambulant myocardial ischemia were studied in a double-blind, randomized, placebo-controlled, crossover trial.

METHODS

This study was approved by the Institutional Review Board at the University of Florida and the Research Committee at the Gainesville Veterans Affairs Medical Center. All patients gave informed consent for participation. The protocol design was conceived by the investigators, and data analyses were performed independently by both ICI Pharmaceuticals and the investigators.

Patients: To be entered into the study, patients had to have a history of typical anginal chest pain and coronary angiograms demonstrating significant coronary artery disease (coronary stenosis $\geq 50\%$ diameter narrowing). Alternatively, if coronary angiography was not performed, a redistribution defect on stress thallium-201 scan in the presence of typical angina and ischemic

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ST-segment changes were considered criteria for both coronary artery disease and ischemia. In addition, all patients had a treadmill exercise test response considered typical for transient myocardial ischemia (≥ 1 mm horizontal ST-segment depression) without symptoms using a modified Bruce protocol within 6 months of study entry. Patients were required to be only minimally symptomatic (Canadian Cardiovascular Society class 1 or 2). Patients were excluded if they had recent myocardial infarction (< 1 month), uncontrolled hypertension, an electrocardiographic abnormality or other conditions (e.g. drugs) that would render the ambulatory electrocardiogram ST-segment monitor uninterpretable, severe congestive heart failure, known hypersensitivity to either study medication or standard contraindications to β -blocker therapy, or were taking calcium antagonists or β blockers.

Study design (Figure 1): The study design was a double-blind, crossover, comparison trial of atenolol and nifedipine. In addition, the combination of these 2 drugs was administered in a single blind fashion to patients refractory to monotherapy.

At the beginning of the study, all antianginal medication was discontinued except sublingual nitroglycerin for relief of angina. Patients were then entered into a 2-week, single-blind, placebo run-in period, at the end of which 48-hour ambulatory electrocardiographic monitoring was performed. To qualify for continuing in the study, patients were required to have either ≥ 5 ischemic episodes or a total duration of ischemia of ≥ 5 minutes during the 48-hour monitoring period.

After the placebo run-in period, qualifying patients entered the first 2-week, double-blind, active treatment period. Patients were randomly assigned to receive either atenolol, 100 mg once each day, or nifedipine, 20 mg 3 times daily, and the corresponding placebo. If limiting side effects occurred after active treatment was initiated, the dosage could be decreased to 50 and 30 mg/day, respectively. After the first active treatment period, patients entered a second 2-week, single-blind, placebo period. This second placebo treatment period was per-

formed to assess for possible spontaneous improvement or worsening of the ischemic variables as a confounding factor. After this second placebo period, patients were crossed over to the alternate active therapy and corresponding placebo and this therapy was continued for 2 weeks. If asymptomatic ischemia was not eliminated during therapy with either active treatment, patients received combination therapy with both agents at the same dose used during the monotherapy treatment periods for an additional 2 weeks.

Ambulatory electrocardiographic monitoring was performed during the last 2 days of each study period. These days were chosen to eliminate any possible carry-over effect from the prior treatment period. Total study duration was 8 to 10 weeks.

Ambulatory monitoring: Ambulatory electrocardiographic monitoring was performed using Oxford FM ambulatory monitors (model 3500). A 2-lead system was used that reflected a modified lead V₅ and lead III. At the time of hook-up, patients were tested using various maneuvers to assess postural and hyperventilation-induced electrocardiographic abnormalities that would affect the specificity of any ST changes noted. Patients were asked to keep a diary detailing occurrence of angina, nitroglycerin consumption, various daily activities and emotional changes. Angina was scored on a scale of $\frac{1}{2}$ to 4 (mild tightness to worst pain ever experienced).

An episode of ischemia was defined as horizontal or downsloping ST-segment depression of ≥ 1 mm lasting for at least 1 minute in either lead. Each episode of ischemia was separated from other episodes of ischemia by a period when the ST segment returned to baseline for at least 1 minute. All recordings were analyzed at the study site by an experienced technician and at least 1 physician investigator.

As a simple measure of variability during a 24-hour period, ischemic parameters were summed into four 6-hour periods, 0600 to 1200, 1200 to 1800, 1800 to 2400, and 2400 to 0600 hours.

Statistical analysis: Only patients who had data available from both active treatment phases were in-

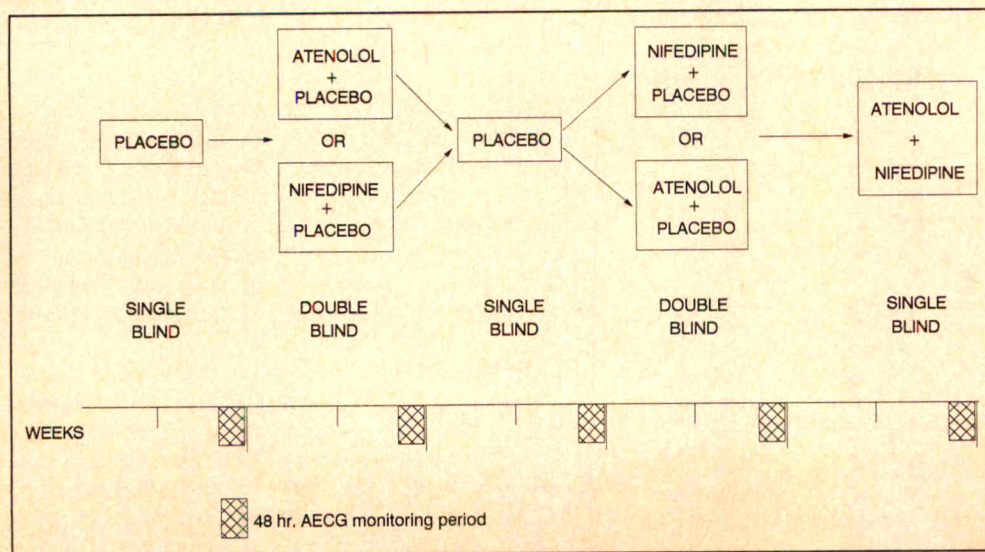


FIGURE 1. Study design. AECG = ambulatory electrocardiography.

TABLE I Patient Characteristics

Pt	Age (yr)	Exercise Stress Test			Percent Diameter Narrowing of Coronary Arteries						
		Time (min)	HR (beats/min)	ST↓ (mm)	Right	LAD	LC	Other	DM	SH	CS
1	76	6	115	1.5		100	95	Diag. 70	+	—	—
2	74	6	140	2		Unknown			+	+	+
3	73	1.5	100	3	100	50	85		—	+	+
4	72	5.5	107	3	100			Septal 90	—	—	+
5	72	9	114	1	80	50	50		—	—	+
6	69	3	100	1	100		50	Diag. 70	+	—	+
7	68	6	138	2.5	100				—	+	+
8	67	5.5	130	2	99	70	100		—	+	+
9	65	6	92	2	100				—	+	—
10	64	4.5	115	2	40	40	100		—	—	+
11	62	7	138	2	100				+	+	+
12	62	3.5	150	3	100	40			—	+	+
13	61	3	110	1.5	60				—	—	+
14	60	12	136	1.7		50	100	Diag. 90	—	+	+
15	57	3	138	2	100	50	80		+	+	+
16	52	6	118	3		70	100	PD 100	—	+	+
17	50	6	106	2	100	60			+	+	—
18	43	3	120	2	60	20	60		—	+	+

CS = cigarette smoking; Diag. = diagonal; DM = diabetes mellitus; HR = heart rate; LAD = left anterior descending; LC = left circumflex; PD = posterior descending; SH = systemic hypertension; ST↓ = ST-segment depression; + = positive; — = negative.

TABLE II Treatment Efficacy During Monotherapy

	Placebo 1	Nifedipine	Atenolol	Placebo 2
No. of episodes	10 ± 2	6 ± 2*	5 ± 1*	10 ± 3
Average duration of episode (min)	22 ± 5	12 ± 3*	9 ± 3*	25 ± 11
Total duration of ischemia (min/48 hours)	245 ± 69	134 ± 51*	90 ± 41	251 ± 105

* $p < 0.05$ compared with placebo.

All data are mean ± standard error of the mean.

Difference not significant for all variables, nifedipine compared with atenolol and placebo 1 compared with placebo 2.

cluded in the statistical analysis. Analysis of baseline differences between the 2 treatment sequence groups was made using 2-sample t tests for continuous measures and exact probability tests for discrete measures. A crossover analysis of covariance was used to evaluate the effects of period and treatment for the ischemic episode-derived variables. Total ischemic episodes and duration for the 6-hour time periods were compared using an analysis of variance for repeated measures. All data are reported as mean ± standard error of the mean. Statistical significance was defined as $p \leq 0.05$.

RESULTS

Patient group: Thirty-nine patients were entered into the first placebo period. Twenty had sufficient ischemia on ambulatory monitoring to qualify and 18 patients completed the study according to protocol. The other 2 patients elected to withdraw from the study after the placebo run-in period because they did not want to repeat 48 hours of continuous electrocardiographic monitoring and not because of any treatment. All subjects were men (mean age ± standard deviation was 63.4 ± 8.6 years [range 43 to 76]). Seventeen of the 18 underwent coronary angiography which revealed severe coronary artery disease. The other patient (no. 2) had a

history of typical angina and a thallium exercise test with a redistribution defect in the inferior wall accompanied by ST-segment depression. Patient 18 was the only other subject who underwent a thallium exercise test, which revealed a reversible defect corresponding to his coronary anatomy. Other pertinent details regarding the patients are summarized in Table I.

Adverse experiences: Seven patients had an adverse effect with nifedipine, 4 with atenolol and 1 with combination therapy. Only 1 of the patients experiencing adverse effects during combination therapy had the dose reduced as a result. All of the other adverse effects were considered minor and either resolved with further treatment or were easily tolerated.

Treatment efficacy: MONOTHERAPY: Data from the placebo and monotherapy periods for the 18 patients who completed all study phases are summarized in Table II. Eight patients were randomized to receive atenolol first and the other 10 to receive nifedipine during the first treatment period. There were no differences in response to therapy related to the order of therapy in number of ischemic episodes, total duration of ischemia, or average duration of each ischemic episode. When atenolol was compared with nifedipine, both agents were associated with similar reductions in number of

TABLE III Ischemic Parameters by Time of Day

	Placebo 1	Nifedipine	Atenolol
Ischemic episodes			
0600-1200	4 ± 0.7	2 ± 0.7*	0.4 ± 0.1*†
1200-1800	3 ± 0.5	2 ± 0.5	1 ± 0.4*
1800-2400	3 ± 0.7	1 ± 0.4*	2 ± 0.7
2400-0600	1 ± 0.4	0.4 ± 0.2	1 ± 0.4
Ischemic duration (min)			
0600-1200	97 ± 26	42 ± 15*	11 ± 8*
1200-1800	50 ± 21	60 ± 24	19 ± 8
1800-2400	74 ± 25	31 ± 17*	45 ± 15
2400-0600	23 ± 12	9 ± 6	25 ± 21

* p < 0.05 versus placebo; † p < 0.05 versus nifedipine.

ischemic episodes, total duration of ischemia and average episode duration. Compared with the initial placebo period, nifedipine was associated with reductions in the number of episodes, the total duration of ischemia and average episode duration. Similar results occurred when atenolol was compared with the initial placebo period; there were reductions in the number of episodes and average episode duration, but the reduction in total duration of ischemia during atenolol compared with placebo was of borderline significance ($p = 0.066$).

Individual responses to therapy were variable (Figure 2). No patient responded completely to both nifedipine and atenolol when they were used as separate monotherapy. Compared with the initial placebo period, during nifedipine therapy, 12 of 18 patients (67%) had $\geq 50\%$ reduction or complete elimination of ischemic episodes and duration of ischemia. Similarly, during atenolol therapy, 12 of 18 patients (67%) had $\geq 50\%$ reduction or complete elimination of ischemic episodes and 15 of 18 patients (83%) had $\geq 50\%$ reduction in ischemia duration. Some patients (4 taking nifedipine and 3 taking atenolol) had more ischemia with drug therapy. Excessive changes in heart rate and blood pressure were not noted during visits in patients experiencing increases in ischemia, making major changes in oxygen requirements unlikely as a potential cause.

Combination therapy: Of the 18 patients who completed the 2 monotherapy phases, only 8 responded to either atenolol or nifedipine alone with complete relief of ambulant ischemia. One of the other 10 patients had complete disappearance of asymptomatic ischemia but had 1 episode of symptomatic ischemia during atenolol therapy and therefore was not entered into the combination therapy phase. The other 9 continued into the combination therapy phase. In these 9, all ischemic episodes were eliminated by combined therapy in 2; 5 others had 50% reduction in number of episodes, 1 had <50% reduction and 1 had no change. However, in all 7 patients who did not have complete relief with combination therapy, the duration of ischemia was reduced $\geq 50\%$.

The characteristics of the ischemia at baseline in patients who responded to monotherapy were compared with those of patients who did not respond. In the responder group, during the baseline placebo period, the number of episodes was 7.7 ± 1.7 , the total duration of ischemia was 159 ± 76 minutes, and the average episode duration was 14.9 ± 4.8 minutes. In the nonresponder group, during the baseline placebo period, the number of episodes was 12.6 ± 3.4 , the total duration of ischemia was 346 ± 112 minutes, and the average episode duration was 32 ± 9.4 minutes. When comparing the groups in terms of these characteristics there were no statistically significant differences despite obvious trends.

Circadian variation: Data from the four 6-hour periods are listed in Table III. There were some minor differences noted but because of the small numbers involved, hourly variability and definite conclusions regarding circadian variability cannot be made.

DISCUSSION

Results of the current study suggest that in a group of minimally symptomatic men with ischemia during normal activities, either atenolol or nifedipine may be effective therapy compared with placebo, but neither is necessarily superior and ischemia may actually increase with either therapy. Also, in patients for whom mono-

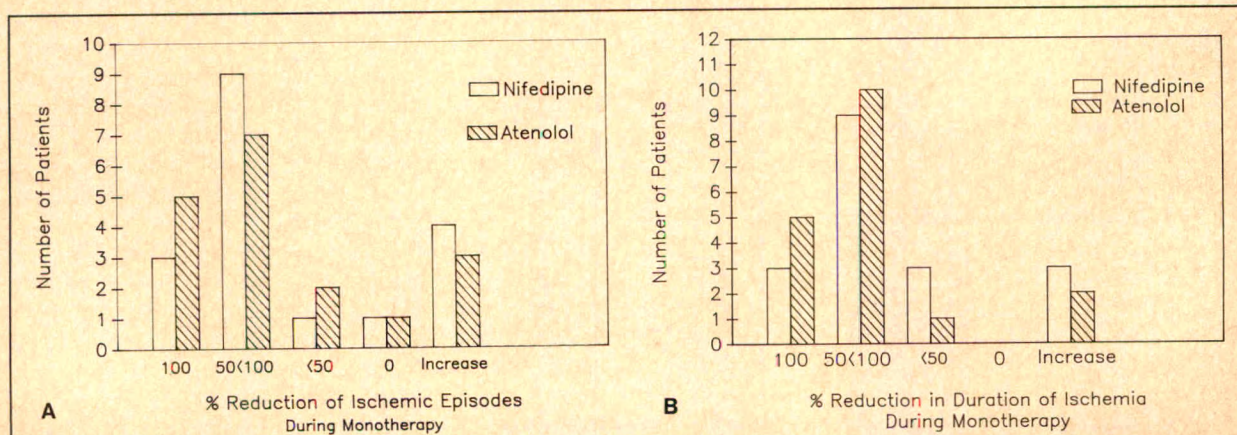


FIGURE 2. A, percent reduction of ischemic episodes during monotherapy. The individual responses to nifedipine and atenolol monotherapy are shown, with the number of patients (vertical axis) experiencing each category of response. B, percent reduction in duration of ischemia during monotherapy. The individual responses to nifedipine and atenolol monotherapy are shown, with the number of patients (vertical axis) experiencing each category of response.

therapy is ineffective in eliminating ambulant ischemia, combination therapy may prove useful. Despite a trend toward more ischemia in the nonresponders, there were no characteristics of the ischemia at baseline that predicted a good response to either monotherapy or the need for combination therapy. Although this has not been previously reported, definitive determination of such characteristics would require a larger sample size.

Other investigators have evaluated the use of both β blockers and calcium antagonists alone for the treatment of myocardial ischemia. Quyyumi et al² evaluated the response to atenolol and nifedipine in 9 patients with ischemic ST depression on the ambulatory electrocardiogram. They administered the same doses of nifedipine and atenolol as in the current study but their patient population was very symptomatic both during exercise and angina at rest. During atenolol treatment, 3 patients had no ischemia and the group as a whole had significantly less ischemia with atenolol than with nifedipine. Contrary to the current study results, no patient's condition was worse with monotherapy than with no therapy. Mulcahy et al,⁵ extending these observations and including some of the data of Quyyumi, reported the responses of 53 patients to treatment with nifedipine, atenolol or the combination on transient ischemia. Atenolol was associated with a significant reduction in both frequency and duration of ischemia, whereas nifedipine had little effect. In this report, other than group data, few comparisons can be made because the specific circumstances of therapy, patient population studied and other details are not clear.

Others have reported the effects of combination therapy on ischemic parameters. Egstrup⁶ evaluated the response of ischemic parameters in 42 patients with chronic stable angina to nifedipine, metoprolol and their combination in a parallel design. Metoprolol was found to decrease total ischemic episodes 55% and duration of ischemia 51%, whereas nifedipine showed no change in either parameter. Combination therapy also reduced the number of ischemic episodes as well as the duration of ischemia significantly better than nifedipine but no better than metoprolol monotherapy. Moreover, there was a small (17%) increase in asymptomatic ischemic episodes with nifedipine.

We found that with both therapies ambulant ischemia may increase, which has been reported previously but not emphasized. Dihydropyridine calcium antagonists have been previously reported to provoke transient myocardial ischemia,⁷ but whether an actual "proischemic effect" occurs with either drug cannot be determined. Cohn et al⁸ investigated the effect of added nifedipine, and found that a 23% reduction in ischemic

episodes occurred in the group as a whole but 43 of 136 (32%) had more episodes, whereas 75 of 136 (55%) had a reduction. This again suggests that the general trend is for improvement in ischemia with nifedipine but that there is considerable individual variability.

Study limitations: There are several important limitations in the current study that deserve comment. First, a small number of highly selected patients were studied over a relatively short time period. The crossover design makes conclusions more valid in a small group but long-term effects cannot be determined. Second, all the subjects were men. Third, there was considerable variability among patients in terms of amount and duration of ischemia. However, this does reflect the characteristics of the population with ambulatory ischemia and those at risk for adverse events.^{1,9} Fourth, to simplify the study design, only fixed doses of the study drugs were given and no attempt was made to titrate to maximal effect. Finally, we cannot be sure that spontaneous variability in ambulant ischemia did not contribute to some of the presumed treatment effect. However, the similarity of the 2 placebo periods and the lack of order effect on ischemia make this possibility less likely.

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Spontaneous Myocardial Ischemia and the Signal-Averaged Electrocardiogram

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The effects of transient myocardial ischemia on the signal-averaged electrocardiogram were investigated in 13 patients with coronary artery disease and spontaneous angina undergoing 3-channel ambulatory electrocardiography. Ischemia was seen as ST elevation in 2 patients or ST depression in 11; it was anterior in 5 patients, inferior in 4 and undefined in 4. Signal-averaged electrocardiograms with noise levels $\leq 1 \mu\text{V}$ were obtained from Holter tapes during 54 of 61 ischemic attacks recorded in the study group (88%), and compared with 54 tracings recorded within 60 minutes of the index attacks. Baseline tracings were normal in 8 patients (62%), showed a long QRS duration in 2 (15%), and both a long QRS duration and a late potential in the remaining 3 (23%). Comparison of recordings at baseline and during ischemic attacks revealed no significant changes in signal-averaged electrocardiographic parameters. Absence of significant differences was also noted when analysis was performed according to the type of ischemic attacks (associated with ST elevation [$n = 14$] or ST depression [$n = 40$]), their location (anterior [$n = 21$] or inferior [$n = 23$]), their duration (>10 minutes [$n = 29$] or ≤ 10 minutes [$n = 25$]), and their magnitude (>2 mm [$n = 18$] or ≤ 2 mm [$n = 36$]). It is concluded that spontaneous transient myocardial ischemia, independent of its type, location, duration and magnitude, does not generate a substrate for late potentials on the signal-averaged electrocardiogram.

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Delayed and fractionated ventricular activation potentials, usually referred to as late potentials, were initially observed on epicardial recordings during experimental myocardial ischemia and infarction and were subsequently documented on body surface signal-averaged electrocardiograms from the laboratory animal as well as in the clinical setting.¹⁻⁵ The ability to reliably record and analyze late potentials from Holter tapes has recently been reported.⁶ In the present study, the technique of signal-averaging from Holter tapes was used to investigate if transient myocardial ischemia resulted in any significant changes in signal-averaged electrocardiographic variables in a group of patients with coronary artery disease and spontaneous angina. Preliminary data have been published.⁷

METHODS

Patients: Candidates for this study were all patients hospitalized with spontaneous angina who underwent a 24-hour ambulatory electrocardiogram in the absence of any therapy except sublingual nitrates if needed. The study group included 13 patients who, in the course of their admission, met the following criteria: (1) presence of ≥ 1 transient myocardial ischemic attack during the ambulatory electrocardiogram; (2) absence of acute (<1 week) myocardial infarction, left ventricular aneurysm, acute or chronic heart failure, life-threatening arrhythmias, electrolyte imbalance, recent antiarrhythmic or β -blocker therapy; (3) QRS duration <120 ms without bundle branch block or QT prolongation on the 12-lead electrocardiogram; (4) documentation of coronary artery disease by angiographic studies (6 patients), history and electrocardiographic criteria of prior myocardial infarction (1 patient), or both (6 patients). Spontaneous angina was present in all patients and was associated with exertional angina in 11.

Ambulatory electrocardiogram: Three-channel ambulatory electrocardiograms were recorded with Del Mar Avionics portable units (model 459) and analyzed with a Del Mar Avionics replay unit (model 750A) equipped with the Micropotential Analyzer option. The recorder had a flat frequency response of 0.1 to 100 Hz ± 3 dB and provided a 1-mV calibration pulse for about 6 minutes at the beginning of each tape, which was used to calibrate the scanner. Patients were instructed to press an "event button" on the recorder in case of chest pain in order to distinguish symptomatic from silent ischemic attacks. Three bipolar leads were used: X lead, with the positive and negative electrodes located, respectively, on the left and right fourth intercostal spaces on the midaxillary line, resembling Holter lead CC5 ("lat-

TABLE I Clinical, Electrocardiographic and Angiographic Variables in 13 Patients with Transient Myocardial Ischemic Attacks During Ambulatory Electrocardiography

Pt.	Age (yr) & Sex	Diagnosis		ST Changes During Ischemia	Coronary Angiographic Data (% Stenosis)				
		MI	Angina		LM	LAD	LC	Right	Grafts
1	55,M	0	M	↓,Y	0	85	0	0	—
2	59,M	A,non-Q	M	↓,Y,X	0	95	0	0	—
3	59,M	0	M	↓,Y,X	0	90	40	50	—
4	58,M	I	M	↓,Y,X	0	70	0	100	—
5	58,M	I	M	↓,Y,X	0	75	50	100	—
6	55,M	0	S	↑,Z	0	0	0	90	—
7	71,F	I,non-Q	S	↑,Z	0	30	40	95	—
8	62,M	0	M	↓,X,Z	0	0	0	99	—
9	56,M	0	M	↓,X,Z	0	0	90	0	—
10	56,M	L,non-Q	M	↓,Y,X	90	0	0	0	—
11	66,M	0	M	↓,X,Y	0	90	80	100	50 (LIMA to LAD)
12	69,M	I,L	M	↓,X	20	100	100	100	50 (SVG to LAD)
13	79,M	I	M	↓,X,Y	—	—	—	—	—

A = anterior; I = inferior; L = lateral; LAD = left anterior descending coronary artery; LC = left circumflex artery; LIMA = left internal mammary artery; LM = left main trunk; M = mixed (spontaneous and exertional); MI = myocardial infarction; S = spontaneous; Right = right coronary artery; SVG = saphenous vein graft; X, Y and Z = ambulatory electrocardiogram leads; 0 = absent; — = not determined; ↑ = elevation; ↓ = depression.

eral" lead); Y lead, with the positive and negative electrodes applied, respectively, at the V3 position and on the manubrium sterni, resembling Holter lead CM3 ("anterior" lead); Z lead, with the positive and negative electrodes applied, respectively, on the sacrum and the manubrium sterni, resembling Holter lead A ("inferior" lead). This configuration represented a modification of the orthogonal system originally described by Simson⁵ and was selected to maximize the detection and analysis of transient myocardial ischemic attacks. ST changes were identified by examining (1) the oscilloscopic replay of the tracing scanned at 120 times real-time; (2) the plots of the ST level and heart rate obtained from all 3 channels; (3) the transcription at a paper speed of 25 mm/s of all parts of the recording judged to be consistent with myocardial ischemia on the basis of the high-speed analysis and the ST level printouts. Ischemic attacks were defined as any episode of transient ST elevation or depression ≥ 1 mm from baseline or from the control level if resting ST-T abnormalities were present, having gradual onset and resolution, and lasting ≥ 1 minute.^{8,9}

Signal-averaged electrocardiogram: Analog signals from the tapes were subjected to digital conversion during high-speed scanning at 120 times real-time, with a 12-bit resolution and at a sampling rate of 694 Hz (real-time equivalent)/channel.⁶ Signals were amplified, averaged and filtered with a bidirectional filter at 25 Hz. The filtered leads were then combined into a vector magnitude $\sqrt{X^2 + Y^2 + Z^2}$ and the QRS onset and offset were determined by computer algorithm. The QRS duration and root-mean-square voltage of the signals in the last 40 ms of QRS (RMS40) were calculated. The duration of low-amplitude signals ($<40 \mu V$) was also measured but not used for analysis. An abnormal signal-averaged electrocardiogram was defined as a recording showing a QRS duration >115 ms, an RMS40 $<25 \mu V$, or both.¹⁰ Late potentials were de-

fined as signals with abnormal RMS40.⁵ Signal-averaged electrocardiograms were obtained during all ischemic attacks. Acquisition of data began after ST changes were ≥ 1 mm, included the peak of ischemic attacks, i.e., the maximum degree of ST elevation or depression, and terminated at the onset of the resolution of ST changes. Baseline signal-averaged electrocardiograms were obtained within 60 minutes of each ischemic attack, at least 20 minutes before the onset or after the resolution of ST changes. Recordings were accepted for analysis if they showed a noise level $\leq 1 \mu V$.

Statistical analysis: Values of the signal-averaged electrocardiographic parameters on recordings performed at baseline and during ischemic attacks were compared using the analysis of variance and Student's *t* test for paired data. A *p* value <0.05 was considered statistically significant. All variables were expressed as mean \pm standard deviation.

RESULTS

The clinical, electrocardiographic and angiographic characteristics of the 13 study patients are listed in Table I. During the ambulatory electrocardiogram, ischemic ST changes appeared on the anterior lead in 5 patients and were concordant with angiographic findings, since these patients had a significant ($>50\%$) stenosis of the left anterior descending coronary artery alone or in combination with an occlusion of the right coronary artery and previous inferior myocardial infarction. Ischemic ST changes appeared on the inferior lead in 4 patients and were also concordant with angiographic findings, since these patients had an isolated significant stenosis of the right coronary artery ($n = 3$) or the left circumflex artery ($n = 1$). The location of ischemia could not be determined in the remaining 4 patients because of the presence of diffuse ST changes or severe coronary artery disease, or the absence of angiographic data.

TABLE II Values of Signal-Averaged Electrocardiographic Parameters at Baseline and During Transient Myocardial Ischemic Attacks Analyzed According to Their Type, Location, Duration and Magnitude

	QRSD (ms)		RMS40 (μ V)	
	Baseline	Ischemia	Baseline	Ischemia
ST elevation (n = 14)	115 \pm 16	116 \pm 18	45 \pm 29	38 \pm 33
ST depression (n = 40)	113 \pm 19	114 \pm 17	40 \pm 28	42 \pm 27
Anterior (n = 21)	113 \pm 18	113 \pm 17	43 \pm 31	44 \pm 31
Inferior (n = 23)	115 \pm 17	116 \pm 18	38 \pm 26	38 \pm 27
Long (>10 minutes) (n = 29)	114 \pm 16	114 \pm 18	39 \pm 32	40 \pm 30
Brief (\leq 10 minutes) (n = 25)	114 \pm 19	114 \pm 17	42 \pm 27	41 \pm 27
Severe (>2 mm) (n = 18)	113 \pm 17	114 \pm 17	44 \pm 31	39 \pm 30
Mild (\leq 2 mm) (n = 36)	114 \pm 17	114 \pm 17	41 \pm 28	43 \pm 29

All values are mean \pm standard deviation. All differences were statistically not significant.
QRSD = high-frequency QRS duration; RMS40 = root-mean-square voltage of last 40 ms of QRS.

Ambulatory electrocardiogram: A total of 61 transient myocardial ischemic attacks was recorded (range, 1 to 9 per patient). Among the 61 ischemic attacks, 43 (70%) were silent and 18 were symptomatic. Transient ischemia manifested as ST elevation in 2 patients and as ST depression in 11 patients. No patients developed ventricular tachyarrhythmias (\geq 3 ventricular premature complexes at a rate of >100 beats/min) related to ischemic attacks.

Signal-averaged electrocardiogram: Baseline signal-averaged electrocardiograms were abnormal in 5 of the 13 study patients (38%). A prolonged QRS duration was seen in 2 patients (15%), and both a prolonged QRS duration and a late potential in 3 patients (23%). Recordings with a noise level $\leq 1 \mu$ V could be obtained during 54 of 61 ischemic attacks (88%); the characteristics of these ischemic attacks are listed in Table II. These 54 recordings were matched for comparison with 54 tracings obtained within 60 minutes of the index ischemic attacks. QRS duration and RMS40 were similar at baseline and during ischemia (114 ± 18 vs 114 ± 17 ms and 41 ± 29 vs $41 \pm 29 \mu$ V, respectively; difference not significant). Noise level and the number of averaged beats were also similar at baseline and during ischemia (0.8 ± 0.2 vs $0.9 \pm 0.3 \mu$ V and 434 ± 119 vs 415 ± 112 beats, respectively; difference not significant). Data were analyzed separately according to the type of ischemic attacks, their location, their duration and their magnitude. None of these comparisons revealed any significant differences regarding QRS duration and RMS40 between baseline tracings and those obtained during ischemia (Table II). All normal recordings at baseline remained normal during ischemia, whereas all recordings with abnormal QRS duration or RMS40 at baseline were also abnormal during transient myocardial ischemia. Figures 1 and 2 show examples of signal-averaged recordings before and during transient myocardial ischemia. The latter was evident as ST elevation in Figure 1 and ST depression in Figure 2. The occurrence of ischemia did not result in any significant changes in the signal-averaged electrocardiographic pa-

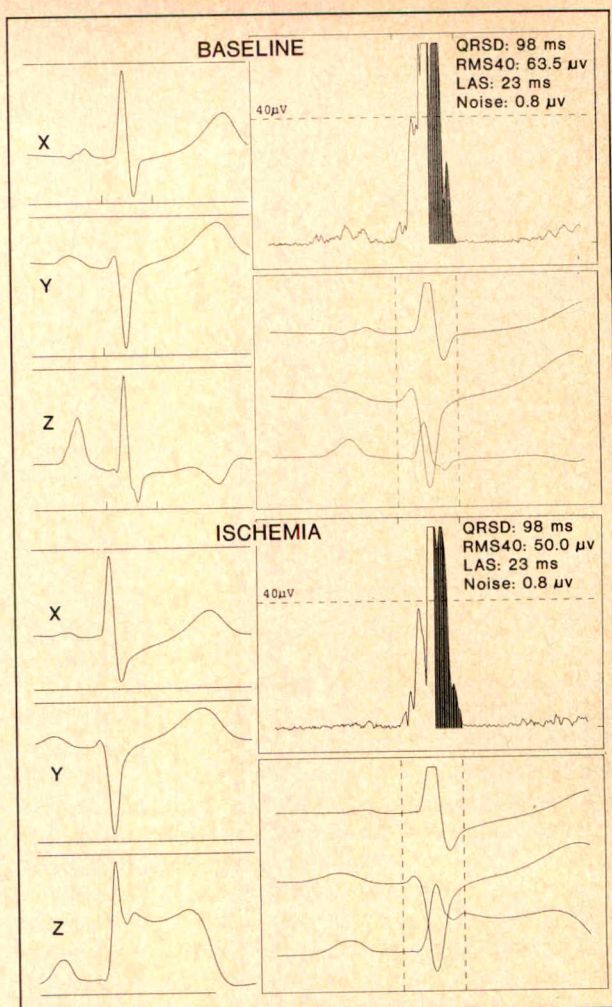


FIGURE 1. Signal-averaged electrocardiograms obtained from Holter tapes in patient 6 at baseline and during transient myocardial ischemia. The latter appears as ST elevation on the Z lead of the 3-channel real-time tracing. Signal-averaged electrocardiographic parameters are normal at baseline and do not show any significant changes during ischemia. LAS = duration of low-amplitude signals $<40 \mu$ V; QRSD = high-frequency QRS duration; RMS40 = root-mean-square voltage of last 40 ms of QRS.

rameters: They were constantly normal in Figure 1 and abnormal in Figure 2.

DISCUSSION

Present study: This study documented the feasibility of obtaining signal-averaged electrocardiograms during episodes of spontaneous transient myocardial ischemia recorded on 3-channel Holter tapes. Our data showed no changes in signal-averaged electrocardiographic parameters between recordings at baseline and during transient myocardial ischemia. An analysis performed according to the characteristics of ischemia (type, location, duration and magnitude) did not change these results: ischemia did not lead to the onset of late potentials, even when it was prolonged and severe.

Previous studies: The effects of transient myocardial ischemia on the signal-averaged electrocardiogram

were the objective of a small number of investigations.¹¹⁻¹³ They focused on ischemia observed during percutaneous transluminal angioplasty,¹¹ dipyridamole test¹² or exercise test.¹³ In a study of Abboud et al,¹¹ a single surface electrocardiographic lead (V₅) was used to compute the RMS voltage of the QRS at a filter setting of 150 to 250 Hz. Ischemia due to angioplasty balloon inflation was reported to cause a significant decrease in the calculated RMS voltage of QRS, as well as the appearance of zones of reduced amplitude in the midportion of QRS. The significance of these findings is uncertain, since they were based on techniques for recording and analyzing the signal-averaged electrocardiogram which were at variance with those used in most recent reports.^{5,10,12-15} In the studies of Turitto¹² and Caref¹³ and their co-workers, serial signal-averaged electrocardiograms were recorded before and during transient myocardial ischemia induced by dipyridamole infusion¹² or by exercise¹³ in patients with documented coronary artery disease and angina. Ischemia did not significantly affect the signal-averaged electrocardiogram: Late potentials failed to appear on tracings obtained during positive dipyridamole or exercise tests. This was independent of the type of ischemia (with ST elevation¹² or ST depression^{12,13}), the presence of abnormal signal-averaged parameters at baseline,^{12,13} the presence and site of previous myocardial infarction,¹³ and the presence of ventricular arrhythmias during ischemia.¹³ On the other hand, some differences between both these reports and the present study must be considered. Induced ischemia was usually brief and relieved by drugs¹² or termination of exercise,¹³ whereas spontaneous ischemia may considerably vary in duration.^{8,9} There may be different pathogenetic mechanisms for provoked and spontaneous ischemia.^{16,17}

Study limitations: The technique of signal-averaging from Holter tapes has inherent problems. Noise levels may be significantly higher than those seen with conventional recording systems; in fact, the mean number of beats required in our study to obtain noise levels $\leq 1 \mu V$ was >400 , an amount that was shown to be associated with noise levels of 0.3 to 0.5 μV on conventional recordings.^{14,15} The inability to achieve low noise levels led to the loss of 12% of our sample of ischemic attacks. Differences in the frequency band width between the conventional and Holter instrumentation result in a tendency toward an increase in QRS duration and a decrease in RMS40 voltage on signal-averaged tracings from Holter tapes.⁶ This issue is not relevant to our study, because each patient represented his own "control." Finally, late potentials may vary in timing and duration and may not be amenable to time-domain signal-averaging, whereas they may be best studied on beat-to-beat recordings.^{18,19}

Despite these limitations, the present study offered evidence that spontaneous transient myocardial ischemia does not affect the signal-averaged electrocardiogram. This confirmed observations relative to laboratory settings^{12,13} and suggests that the electrophysiologic changes associated with ischemia do not represent a

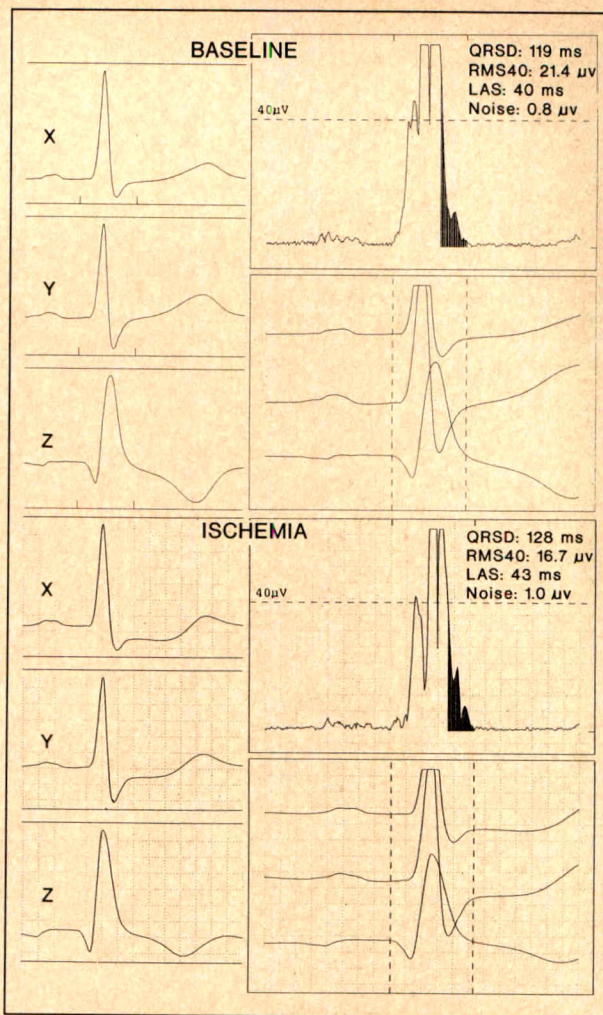


FIGURE 2. Signal-averaged electrocardiograms obtained from Holter tapes in patient 4 at baseline and during transient myocardial ischemia. The latter appears as ST depression on the X and Y leads of the 3-channel real-time tracing. Signal-averaged electrocardiographic parameters are abnormal at baseline and do not show any significant changes during ischemia. Abbreviations as in Figure 1.

substrate for late potentials on the signal-averaged electrocardiogram.

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Right Ventricular Systolic Function During Exercise With and Without Significant Coronary Artery Disease

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To evaluate the effects of exercise and coronary artery disease on right ventricular (RV) systolic function, rest and exercise biplane RV angiograms were recorded in 20 patients undergoing diagnostic cardiac catheterization. Thirteen patients had exercise angiograms of sufficient quality to undergo analysis and were classified into 2 groups. Group 1 had no or only mild coronary artery disease; group 2 had significant coronary artery disease as manifested by new, exercise-induced, left ventricular regional wall motion abnormalities. RV systolic pressure increased in both groups during exercise: 33 to 57 mm Hg in group 1 ($p = 0.0002$) and 33 to 55 mm Hg in group 2 ($p = 0.0004$). Pulmonary resistance did not change in group 1 during exercise but increased in group 2 (3.2 to 4.8 Wood units, $p = 0.04$). RV ejection fraction increased slightly, but not significantly, during exercise in group 1, but decreased in group 2 (73 vs 58% with exercise [$p = 0.01$]). The change in RV ejection fraction from rest to exercise correlated closely with the change in pulmonary resistance from rest to exercise ($r = -0.89$, $p < 0.0001$). RV regional wall motion analysis demonstrated a generalized decline in regional ejection fraction in group 2 during exercise, even in patients without right coronary artery disease. In conclusion, there is a decline in RV ejection fraction during exercise in patients with significant coronary artery disease. The generalized reduction in regional RV ejection fraction coupled with the close correlation with the change in pulmonary resistance suggests that increased afterload, rather than RV ischemia, is the cause.

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The left ventricular response to exercise has been the object of intense study for decades. Right ventricular (RV) function during exercise has also been evaluated, although to a lesser extent.¹⁻³ Frequently, these investigations have reported the hemodynamic response to exercise or RV volumetric changes as assessed by radionuclide techniques.⁴⁻⁶ Angiographic RV evaluation during exercise has been infrequent.^{7,8} Because contrast angiography remains the "gold standard" for ventricular volumetric analysis,^{9,10} we studied the RV systolic response to exercise as evaluated with biplane angiography.

METHODS

Patients: Twenty men underwent right- and left-sided diagnostic cardiac catheterization with biplane right ventriculography at rest and during supine bicycle exercise. Seven patients were excluded from analysis because of poor ventricular opacification during exercise, frequent ventricular premature complexes, unsuspected noncoronary heart disease, or prior coronary artery bypass surgery. The 13 remaining patients are the subject of this report. The patients were subdivided according to coronary anatomy and left ventricular regional wall motion analysis. Six patients (group 1, mean age \pm standard deviation 52 ± 6 years) had no or only functionally mild coronary artery disease (2 with no coronary disease, 2 with $\leq 50\%$ stenoses in major coronary branches, and 2 with occlusions of small diagonal or obtuse marginal branches but no disease in the major coronary vessels). None of these patients had significant LV regional wall motion abnormalities with exercise (Table I).

Seven patients (group 2, mean age 52 ± 8 years) had significant coronary artery disease, defined as $\geq 70\%$ narrowing in a major coronary branch (3 had 1-vessel, 2 had 2-vessel and 2 had 3-vessel disease). Additionally, 6 of the 7 patients in group 2 had a prior myocardial infarction (3 with inferior, 2 with anterior, and 1 patient with both inferior and anterior infarctions). All patients in group 2 had new or worsening LV wall motion abnormalities with exercise (Table I).

Cardiac catheterization: All patients gave informed consent and the Institutional Review Committee for Human Research approved the exercise portion of the protocol. Cardiovascular medications were withheld, except for sublingual nitroglycerin, 12 to 24 hours before the investigation. One hour before catheterization, 10 mg of oral chlorthalidone was given to the patients for sedation. All catheters were introduced transfem-

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TABLE I Regional Left Ventricular Wall Motion Analysis (Right Anterior Oblique Projection) Change in Regional Ejection Fraction from Rest to Exercise

	Post. Basal	Diaphrag.	Apical	Ant. Lat.	Ant. Basal
Group 1	10.0	12.8	4.5	3.4	0.2
Group 2	-4.0	-0.5	-6.4	-2.6	3.0

Regional ejection fraction for 5 sectors of the right anterior oblique left ventriculogram were calculated at rest and for exercise. The data represent the difference (exercise-rest) in ejection fraction (%) for each sector.
Ant. = anterior; Diaphrag. = diaphragmatic; Lat. = lateral; Post. = posterior.

rally. RV pressures were measured with an 8Fr Millar micromanometer pigtail catheter calibrated against a fluid-filled system. Simultaneous left ventricular pressure was obtained from a standard pigtail angiographic catheter. These pressures were recorded (Electronics for Medicine VR 16) at a paper speed of 250 mm/s. A simultaneous electrocardiogram, right and left ventricular pressures and an intracavitary RV phonocardiogram were transcribed.

Biplane right ventriculograms were filmed in the 30° right anterior oblique and 60° left anterior oblique projections at 50 frames/s. Fifty ml of iopamidol (Iopamiro®), a nonionic contrast medium, was injected at a rate of 12 ml/s. A nonionic contrast agent was chosen so that repeat ventriculography would not unduly affect RV hemodynamics.¹¹ Filming was continued to obtain a levophase left ventriculogram. Cine frames were numbered, with corresponding cine markers on the pressure tracing.

Routine left ventriculography and coronary angiography were performed before right ventriculography in order to select patients appropriate for the study as well as to exclude patients with severe or unstable lesions from a prolonged investigation.

Exercise protocol: Standard bicycle exercise ergometry was performed in all patients before catheterization to determine exercise tolerance and angina threshold. During catheterization the patients' feet were elevated and strapped to the pedals of a bicycle ergometer on the catheterization table. All pressures and volumes at rest and during exercise were thus obtained with the legs in the elevated position. There was a 12-minute waiting period between the resting angiogram and the initiation of exercise. Exercise consisted of 2 exercise periods of 2 minutes beginning at 50 to 80 W (mean 68) and con-

tinuing at 70 to 150 W (mean 93). These exercise steps were chosen according to the prior exercise test. At the end of the second period RV angiography was immediately performed. Seventy ml of contrast material was injected at a rate of 14 to 16 ml/s for the exercise ventriculogram.

Right ventricular volume analysis: To determine RV volume angiographically, 15 acrylic radiopaque casts of canine and human right ventricles were constructed. The water displacement volume of these casts were paired with their angiographically derived volume using Simpson's method. A regression equation from this comparison ($\text{volume}_{\text{corr(ml)}} = 0.77 \cdot \text{angiographic}_{\text{vol}} - 12$) was then used to correct the angiographically derived volumes. The details of this procedure are published elsewhere.¹²

Hemodynamic data: Peak RV systolic pressure, RV pressure during each cine frame (every 20 ms) and left ventricular end-diastolic pressure were measured. Because it was not possible to measure RV and pulmonary artery pressures simultaneously, these were estimated in the following fashion: Peak RV pressure was substituted for pulmonary artery systolic pressure since no patient had evidence of pulmonic stenosis. Left ventricular end-diastolic pressure was used as an approximation of pulmonary artery diastolic pressure. Mean pulmonary artery pressure was then calculated as: mean pulmonary artery disease = [peak right ventricular systolic pressure + 2 (left ventricular end-diastolic pressure)]/3. This value was divided by the stroke volume multiplied by the heart rate to calculate an estimate of pulmonary resistance.

The systolic portion of the pressure curve was digitized for the determination of the maximal rate of pressure change (dP/dt) which was calculated every 3 to 5 ms depending on the heart rate. Frame-by-frame RV volume analysis was performed from end diastole to end systole at rest and during exercise. End diastole was defined as the onset of the rapid pressure increase in the RV pressure tracing. End systole was determined as the point of closure of the pulmonic valve as determined angiographically or from the phonocardiogram. RV ejection fraction was calculated in the standard fashion. Additionally, RV ejection rates were calculated for every 20 ms period during systole. To reduce error due to "noise" in the ventricular tracings,¹³ the volumes were initially smoothed with a fifth grade moving average:

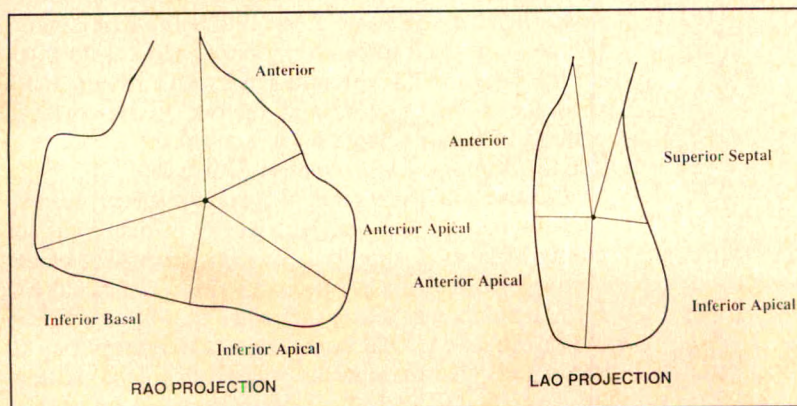


FIGURE 1. Right ventricular regional wall motion analysis was performed by subdividing end-diastolic and end-systolic projections into 4 equiangular sectors, excluding the tricuspid and pulmonic valves. LAO = left anterior oblique; RAO = right anterior oblique.

TABLE II Hemodynamic Data

Pt. No.	HR (beats/min)		RVSP (mm Hg)		LVEDP (mm Hg)		Pul. Resis. (mm Hg·m/liter)		MaxdP/dt (mm Hg/s)	
	R	EX	R	EX	R	EX	R	EX	R	EX
Group 1										
1	100	147	28	47	14	17	2.6	2.2	315	842
2	76	115	34	59	18	30	2.7	2.8	394	648
3	60	102	31	58	16	28	2.8	3.0	267	790
4	71	119	32	57	26	30	3.7	2.6	239	776
5	85	125	35	52	21	30	2.9	3.9	474	590
6	55	107	36	70	20	32	3.5	4.1	336	911
	75 ± 17	119 ± 16	33 ± 3	57 ± 8	19 ± 4	28 ± 5	3.0 ± .5	3.1 ± .5	338 ± 86	760 ± 120
p	0.0001		0.0002		0.004		NS		0.003	
Group 2										
1	79	127	29	51	18	17	2.6	2.3	539	1,492
2	88	137	35	70	21	43	3.6	5.5	482	969
3	65	90	29	39	21	32	3.7	3.7	289	567
4	88	131	36	52	10	29	3.2	4.4	566	766
5	71	112	26	57	12	42	2.6	6.7	316	1,029
6	61	147	37	61	8	35	3.0	6.5	448	784
7	86	122	37	58	16	25	3.5	4.2	478	1,030
	77 ± 11	124 ± 19	33 ± 5	55 ± 10	15 ± 5	32 ± 9	3.2 ± .5	4.8 ± 1.6	445 ± 106	948 ± 293
p	0.0006		0.0004		0.026		0.04		0.0006	
Group 1 Versus Group 2										
	NS	NS	NS	NS	NS	NS	NS	0.04	NS	NS

Hemodynamic data for groups 1 and 2 at rest and exercise. Parameters for each patient are given along with the mean ± standard deviations and p values of the differences. EX = exercise; HR = heart rate; LVEDP = left ventricular end-diastolic pressure; MaxdP/dt = maximal rate of pressure change; NS = not significant; Pul. Resis. = pulmonary resistance; RVSP = right ventricular systolic pressure.

$V(t) = [v(t - 40) + 2v(t - 20) + 3v(t) + 2v(t + 20) + v(t + 40)]/9$, where t is the time from pulmonic valve opening in ms and $v(t)$ and $V(t)$ are raw and smoothed RV volumes, respectively. These data were then normalized for body surface area. The ejection rate was calculated as: ejection rate (ml/m²/s) = $[V(t + 20) - V(t - 20)]/40$ ms. The peak ejection rate was taken as the maximal flow velocity during the ejection period.

Regional ejection fraction was calculated from RV cine frames at rest and during exercise. Both the right anterior oblique and left anterior oblique projections were subdivided into 4 equiangular quadrants (Figure 1) through the center of gravity of each silhouette. The area of each quadrant was measured and the reduction in area from end diastole to end systole was divided by the end-diastolic area to obtain the regional ejection fraction.

In a similar fashion, the right anterior oblique left ventricular end-diastolic and end-systolic cine frames were subdivided into 6 areas and regional ejection fractions were calculated at rest and during exercise to evaluate left ventricular wall motion abnormalities (Table I).

Statistical methods: Intragroup comparisons were obtained using a paired Student's t test, and intergroup comparisons with the unpaired t test. Linear regression analysis was performed using Statview™ software.

RESULTS

Hemodynamic and volumetric data for the 2 groups are listed in Tables II and III. There were no significant differences between resting values in the 2 groups, al-

though there was a tendency for RV ejection fraction to be lower in group 2.

In groups 1 and 2, heart rate, peak RV systolic pressure, peak dP/dt and peak ejection rate increased with exercise.

There were significant differences between groups 1 and 2 with exercise. Stroke volume index was significantly different between groups 1 and 2 ($p = 0.02$) during exercise. Pulmonary resistance was higher during exercise in group 2 than in group 1 ($p = 0.04$). RV ejection fraction was substantially different between the 2 groups. Finally, peak ejection rate during exercise was higher in group 1 than in group 2 ($p = 0.03$).

The results of RV regional wall motion analysis are summarized in Table IV. In group 1, there tended to be a generalized increase in regional ejection fraction from rest to exercise. Conversely, in group 2, regional ejection fraction was generally lower with exercise, decreasing or remaining the same in 8 of 8 sectors.

The change in RV ejection fraction from rest to exercise correlated closely with the change in pulmonary resistance in the 2 groups ($r = -0.89$, $p < 0.0001$) (Figure 2).

DISCUSSION

In this study we evaluated angiographically the effects of exercise on RV function in patients with and without coronary artery disease. In both groups, RV systolic pressure and peak dP/dt increased similarly with exercise. However, patients with coronary artery disease had a significantly lower stroke volume and ejection fraction with exercise than the normal group.

TABLE III Volumetric Data

TABLE III. Volumetric Data										
Pt. No.	EDVI (ml/m ²)		ESVI (ml/m ²)		SVI (ml/m ²)		RVEF (%)		PER (ml/m ² /s)	
	R	EX	R	EX	R	EX	R	EX	R	EX
Group 1										
1	52	58	12	11	40	47	77	81	184	282
2	102	101	36	30	66	71	65	70	258	388
3	87	78	20	11	67	67	77	86	271	345
4	74	82	22	20	52	62	70	76	211	330
5	69	57	19	20	50	37	72	65	147	203
6	108	89	34	35	74	54	69	61	293	283
	82 ± 21	78 ± 17	24 ± 9	21 ± 10	58 ± 13	56 ± 13	72 ± 5	73 ± 10	227 ± 56	305 ± 64
p	NS		NS		NS		NS		0.01	
Group 2										
1	85	80	33	26	52	54	61	68	276	362
2	65	74	20	35	45	39	69	53	213	209
3	79	82	31	34	48	48	61	59	170	198
4	55	58	21	26	34	32	62	55	219	147
5	79	76	23	36	56	40	71	53	266	211
6	79	59	23	32	56	27	71	46	246	129
7	57	51	19	15	38	36	67	71	236	201
	71 ± 12	69 ± 12	24 ± 5	29 ± 7	47 ± 9	39 ± 9	66 ± 5	58 ± 9	232 ± 36	208 ± 75
p	NS		NS		NS		NS		NS	
Group 1 Versus Group 2										
	NS	NS	NS	0.12	NS	0.02	0.05	0.01	NS	0.03
Volumetric data for groups 1 and 2 at rest and during exercise. Mean ± standard deviations and p values are given below each column. EDVI = right ventricular end-diastolic volume index; ESVI = right ventricular end-systolic volume index; PER = peak right ventricular ejection rate; RVEF = right ventricular ejection fraction; SVI = stroke volume index; other abbreviations as in Table II.										

Volumetric data for groups 1 and 2 at rest and during exercise. Mean ± standard deviations and p values are given below each column. EDVI = right ventricular end-diastolic volume index; ESVI = right ventricular end-systolic volume index; PER = peak right ventricular ejection rate; RVEF = right ventricular ejection fraction; SVI = stroke volume index; other abbreviations as in Table II.

RV ejection fraction correlated closely with changes in RV afterload from rest to exercise.

The hemodynamic changes produced by exercise in the right ventricle and pulmonary circulation have been well described.^{1,14-16} In evaluating these data, it is important to be cognizant of body position during the exercise (supine with legs down or elevated, or sitting) and also the age of the patient group studied. In most studies, pulmonary artery systolic pressure increases significantly in both normal subjects and patients with coronary artery disease during supine exercise.¹⁶

Peak dP/dt has been infrequently evaluated in the right ventricle. Bussmann et al⁸ reported a mean peak dP/dt of 490 mm Hg/s in 17 patients with left anterior descending coronary artery disease and 350 mm Hg/s in 9 patients with right coronary artery disease. In both groups, peak dP/dt increased significantly with exercise. However, there are theoretical concerns when peak dP/dt is used as an index of RV contractility.¹⁷ Contrary to peak left ventricular dP/dt, which precedes aortic valve opening, peak dP/dt of the right ventricle customarily occurs after the pulmonic valve opens. Moreover, it is an "impure signal" influenced by the timing of left ventricular contraction.¹⁸

A number of investigators have determined RV volumes angiographically. They have employed Simpson's rule,^{19,20} as in our own study, or geometrical approximations of RV shape.^{21,22}

Radionuclide determined RV end-systolic and end-diastolic volumes have generally been reported to be larger, and the ejection fraction smaller, than those

found with contrast angiography.^{5,6} This discrepancy has been thoroughly evaluated by Marving et al.¹⁰ They conclude that a major reason for this is the difficulty in discerning the RV-right atrial border, and therefore only right anterior oblique projections should be used in radionuclide RV investigations. Dell'Italia et al²³ found a close correlation, $r = 0.91$, between angiographic and radionuclide-determined RV volumes; however, a geometric correction for attenuation was applied and a close correlation would not exclude a consistent overestimation in ventricular volume.

Determinants of right ventricular ejection performance during exercise: What is the mechanism for the decline in RV ejection fraction during exercise in patients with coronary artery disease? Many factors may be involved, including RV ischemia, septal shifting and loading of the right ventricle. In radionuclide exercise studies reported by Johnson⁵ and Maddahi⁶ and their co-workers, RV ejection fraction failed to increase during exercise when there were significant right coronary artery lesions. RV ejection fraction has been shown to decline when the right coronary artery is occluded during percutaneous transluminal coronary angioplasty.²⁴ In 5 of the 7 patients in group 2, there were significant lesions involving the right coronary artery, so exercise-induced ischemia could result in RV dysfunction. However, in the 2 other patients (patients 3 and 5, group 2, Table III) without significant right coronary artery disease, RV ejection fraction also decreased during exercise. Septal asynergy was not seen in group 2 (Table IV), so it is unlikely that septal ischemia is responsible.

TABLE IV Right Ventricular Wall Motion Analysis

Pt. No.	Right Anterior Oblique				Left Anterior Oblique			
	ANT	ANT-API	INF-API	INF BSL	ANT	ANT-API	INF-API	SUP-SEP
Group 1								
1	9	-1	4	23	5	-9	-2	40
2	2	9	0	-6	17	4	-1	-62
3	20	2	16	15	31	31	27	27
4	4	8	6	4	19	10	10	-3
5	0	8	15	-1	-8	-14	2	-15
6	-15	9	5	-8	-13	-8	-13	7
	3.3 ± 11	5.8 ± 4.3	7.7 ± 6.4	4.5 ± 12.2	8.5 ± 17	2.3 ± 17	3.8 ± 14	-1 ± 36
Group 2								
1	6	-10	3	-9	3	10	8	13
2	-21	-19	2	-2	-17	-8	-15	-5
3	-10	8	13	-11	5	6	-1	-3
4	-3	-21	2	-10	-10	6	0	-1
5	-22	-38	-23	-17	-54	-14	-4	-9
6	-22	-28	-25	-24	-43	-12	-30	-25
7	10	21	-22	-10	-8	-3	3	30
	-8.9 ± 14	-12.4 ± 21	-7.1 ± 16	-11.9 ± 23	-17 ± 23	-2.1 ± 9.6	-5.6 ± 13	0 ± 7
Group 1 Versus Group 2								
p	0.11	0.06	0.05	0.01	0.04	NS	NS	NS

Regional wall motion analysis for the right ventricle at rest and during exercise for each of the 8 sectors in both projection. Mean ± standard deviations and p values are given below each column. Note that in group 1, mean regional ejection fraction (%) increased in all sectors as opposed to group 2 where it decreased in 7 of the 8 sectors.

ANT = anterior; ANT-API = anterior apical; INF-API = inferior apical; INF-BSL = inferior basal; NS = not significant; SUP-SEP = superior septal. See Figure 1.

Regional wall motion analysis showed reduced function of the RV free wall during exercise even in patients without significant right coronary artery disease.

Ventricular interaction should also be considered in this reduction of RV systolic function. The left ventricular end-diastolic volume increases with significant ischemia,²⁵ and this may impede RV filling and thus reduce systolic performance. RV end-diastolic volume was mildly, although not significantly, reduced with exercise in group 2. However, there was a similar nonsignificant decline in group 1 without a change in RV ejection fraction.

Another explanation for the decline in RV ejection fraction during exercise is an acute increase in afterload. In group 1, afterload, measured by pulmonary resistance, did not change with exercise, whereas ejection fraction increased slightly but not significantly. However, in group 2, afterload increased and ejection fraction tended to decrease with exertion. There was a close correlation between the change in ejection fraction with exercise and the change in pulmonary resistance (Figure 2).

The correlation between RV ejection fraction and pulmonary hemodynamics during exercise has been reported before, although only in patients with pulmonary or valvular heart disease. Cohen et al² studied 8 patients with mitral stenosis by radionuclide imaging. They found a moderate correlation ($r = -0.71$, $p = 0.05$) between the change in RV ejection fraction from rest to exercise, corrected for duration of exercise, and peak exercise pulmonary pressure. In patients with chronic obstructive pulmonary disease, Morrison et al²⁶ noted a weak correlation ($r = -0.51$, $p < 0.05$) between the change in ejection fraction with exercise and the change in total pulmonary resistance. However, this same

group²⁷ failed to find such a correlation when a mixed group of patients with mitral or aortic stenosis underwent exercise. The difficulties inherent in using radionuclide imaging for RV ejection fraction determination, especially during exercise, may explain the somewhat higher correlation found in our patients.

The influence of pulmonary artery pressures on RV function is a form of ventricular interaction that may have important clinical implications. Even with significant left ventricular failure and elevated resting systemic vascular resistance, systemic vascular resistance de-

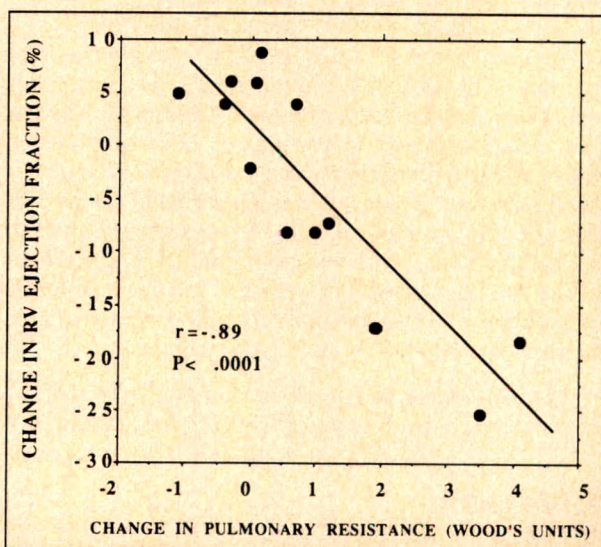


FIGURE 2. Relation of the change in right ventricular (RV) ejection fraction with the change in pulmonary resistance from rest to exercise for groups 1 and 2. Right ventricular ejection fraction tended to decrease as pulmonary resistance increased with exercise.

clines with exercise.²⁸ When significant pulmonary, valvular or coronary artery disease is present, however, pulmonary resistance may increase with exercise and thus impair RV systolic function. In an intriguing report regarding patients with left ventricular dysfunction, Baker et al²⁹ found no correlation between maximum oxygen uptake during exercise and resting left ventricular ejection fraction. Yet there was a good correlation between resting RV ejection fraction and maximal oxygen uptake ($r = 0.70$, $p < 0.001$). When only patients with ischemic cardiomyopathy, and hence more similar to our patients, were considered, this correlation was even stronger ($r = 0.88$, $p < 0.001$).

Thus, elevated left ventricular filling pressures, by increasing pulmonary pressures, may adversely affect RV systolic performance. In a sense, left ventricular diastolic function may influence RV systolic function. Whether this ultimately impairs exercise capability by a reduction in stroke volume is not clear, but deserves closer study.

Study limitations: The current study is limited in a number of ways. First, the number of patients studied was small. Pulmonary resistance was not measured directly in the study but estimated. Accurate pulmonary artery pressures would have required a second catheter to traverse the tricuspid valve, with the likelihood of inducing significant tricuspid regurgitation as well as requiring a second vascular access site. For these reasons an estimation was used. The mean value for pulmonary resistance of 3.0 Wood units obtained for group 1 is near the value of 2.6 reported for normal subjects.³⁰

Second, RV wall stress would be a better measure of afterload than total pulmonary resistance. However, no standard formula has been developed to quantify RV stress, perhaps because this ventricle is more geometrically complex than the left ventricle. Moreover, measurements of wall stress would require the determination of RV wall thickness, which is quite difficult; also, quantitating these changes throughout systole, especially during exercise, was not technically feasible.

Another concern is that the RV angiograms were recorded after contrast administration. However, this was a very involved and strenuous protocol for the patients who consented to participate. We therefore excluded patients from the protocol if severe coronary artery disease was present. A waiting period of 15 minutes after the last coronary injection to review the films and to place the Millar catheter minimized the acute effects of the contrast injections. Finally, nonionic contrast agents such as iopamidol produce fewer hemodynamic changes compared with more standard agents.¹²

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Coronary Collateral Circulation in Coronary Artery Disease and Systemic Hypertension

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The extent and functional capacity of coronary collateral circulation in patients with systemic hypertension has not been elucidated. In the present study, 313 patients with coronary artery disease were studied to evaluate coronary collateral circulation in relation to the presence of systemic hypertension and left ventricular hypertrophy. Patients had $\geq 95\%$ diameter luminal obstruction of either the left anterior descending or the right coronary artery. Patients were classified into 2 groups: The hypertensive group consisted of 61 patients, mean age 55 ± 9 years, with systemic hypertension, and the normotensive group consisted of 252 patients, mean age 53 ± 8 years, without hypertension. The hypertensive group had more severe angina pectoris and less history of healed myocardial infarction than the normotensive group ($p < 0.001$). Left ventricular wall thickness was 1.26 ± 0.1 cm in the hypertensive and 1.03 ± 0.06 cm in the normotensive group ($p < 0.001$). The hypertensive group had more extensive coronary collateral circulation than the normotensive group ($p < 0.01$). There was a positive relation between coronary collateral circulation and left ventricular wall thickness ($p < 0.001$). These results indicate that patients with systemic hypertension and coronary artery disease have an increase in coronary collateral circulation corresponding to the degree of left ventricular wall thickness.

(Am J Cardiol 1991;67:687-690)

Systemic hypertension is associated with an increased susceptibility to coronary artery disease and is the most common cause of left ventricular hypertrophy in adults.¹ Studies in animals and humans indicate that the major conduit of epicardial coronary arteries is enlarged in hypertrophied ventricles.^{2,3} However, this dilatation may be less than what would be expected.³ Minimal coronary resistance assessed by a variety of techniques was abnormally elevated in several animal preparations of cardiac hypertrophy.⁴⁻⁶ The effect of left ventricular hypertrophy due to systemic hypertension on coronary collateral circulation has not been elucidated in humans. In the present study, we investigated the occurrence of coronary collateral circulation detected by angiography in hypertensive patients having total or subtotal occlusion of the left anterior descending or the right coronary artery, and compared them with another normotensive group of patients having the same angiographic findings.

METHODS

Study population: We investigated 4,500 consecutive patients with coronary artery disease who underwent diagnostic coronary angiography and left ventriculography. Patients with cardiomyopathy, valvular or congenital heart disease were excluded from the study. Three hundred thirteen patients had $\geq 95\%$ diameter luminal obstruction of the right coronary artery or the left anterior descending artery. These patients formed the studied group. The contralateral and the circumflex arteries had $< 70\%$ stenosis. All patients had dominant right coronary arteries.

Patients were classified into 2 groups: those with and without systemic hypertension. The hypertensive group consisted of 61 patients undergoing treatment for hypertension and the normotensive group consisted of 252 patients without systemic hypertension (Table I). Initial blood pressure was defined as the pressure before the initiation of antihypertensive treatment. Blood pressure was measured with a standard cuff sphygmomanometer. In each patient 2 blood pressure measurements were obtained at times more than 1 week apart and the measurements were averaged. If the first 2 pressure readings differed by > 5 mm Hg, additional readings were obtained. The diagnosis of systemic hypertension was made if the diastolic pressure was ≥ 90 mm Hg or the systolic pressure was ≥ 150 mm Hg, or both. Blood pressure after treatment was defined as the blood pressure that was found the month before cardiac catheterization. Antihypertensive therapy was continued

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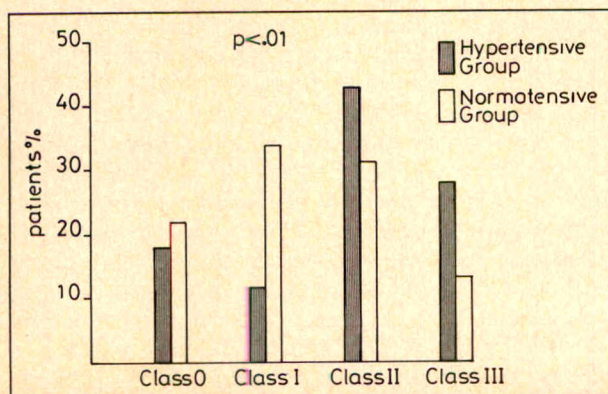
TABLE I Clinical Characteristics and Risk Factors in the Two Groups

	Hypertensives (61 patients)	Normotensives (252 patients)
Age (years)	55 ± 9	54 ± 8
Men:women	52:9	242:10
Right coronary artery (≥95% diameter stenosis)	41 (67%)	113 (45%)*
Left anterior descending (≥95% diameter stenosis)	20 (33%)	139 (55%)*
Serum total cholesterol >250 mg/dL	33 (54%)	122 (48%)
Cigarette smoking	56 (92%)	204 (80%)
Diabetes mellitus	16 (26%)	49 (20%)
Positive family history for coronary artery disease	13 (21%)	50 (20%)
Blood pressure:		
Initial systolic (mm Hg)	172 ± 6	—
Initial diastolic (mm Hg)	102 ± 5	—
Posttreatment systolic (mmHg)	152 ± 5	117 ± 3 [†]
Posttreatment diastolic (mm Hg)	90 ± 4	77 ± 3 [†]
Duration of treatment (years)	5 ± 2	—
Duration of angina pectoris or other forms of coronary artery disease (months)	16.5 ± 10	14 ± 8
Echocardiographic measurements (in 48 patients)	(in 48 patients)	(in 90 patients)
left ventricular wall thickness (cm)	1.26 ± 0.10	1.03 ± 0.06 [†]

* Significantly different in the 2 groups ($p < 0.01$)[†] Significantly different in the 2 groups ($p < 0.001$)

throughout the study period, the time of first appearance of coronary artery disease (angina pectoris, myocardial infarction or sudden death) and the period in months from this time until the cardiac catheterization were recorded. Serum total cholesterol was measured in every patient in the nonfasting state. Cholesterol levels >250 mg/dl were classified as high.

Echocardiography: Echocardiography was performed using an Irex system III phased-array ultrasound unit with a 2.5-MHz transducer and an aperture size of 16 mm. M-mode echocardiographic recordings were performed the day after cardiac catheterization in the last 138 patients studied. The recordings were then coded and analyzed by a second investigator who was unaware of the clinical characteristics of the subject.

**FIGURE 1.** Coronary collateral circulation in the 2 groups. Collateral circulation was more extensive in the hypertensive group.**TABLE II** Clinical Presentation of the Studied Patients

	Hypertensives (61 patients)	Normotensives (252 patients)
History of acute myocardial infarction (%)	27 (44)	174 (70)*
Angina class by NYHA		
I (%)	2 (3)	58 (23)*
II (%)	17 (28)	87 (35)*
III (%)	19 (31)	75 (30)*
IV (%)	23 (38)	32 (13)*

* $p < 0.001$.

NYHA = New York Heart Association functional classification.

Left ventricular wall thickness was measured distal to the tips of the mitral valve leaflets and at the peak of the R wave of the electrocardiogram. Measurements were made over 3 consecutive cardiac cycles and mean values were calculated.

Angiography and grading of collateral circulation:

Two cardiologists unaware of all other clinical characteristics qualitatively assessed the degree of luminal diameter stenosis of the coronary arteries and the collateral filling of the diseased artery. The percent diameter narrowing was calculated from the projection that showed the most severe stenosis and a caliper was used for the estimation. Each cardiologist examined all the films. If there was a disagreement another observer was invited to examine the film, and the majority decided.

Collateral filling of the obstructed vessel was classified based on the presence and extent of epicardial filling by contralateral coronary artery injection,⁹ as follows: class 0, no epicardial filling; class I, filling of side branches only; class II, partial filling of the epicardial segment; and class III, complete filling of the epicardial segment.

Statistical analysis: All parametric data (age, blood pressure and echocardiographic measurements) are expressed as mean ± standard deviation. Differences between groups were calculated with a 2-tailed *t* test or chi-square test after Yates' correction. Probability <0.05 was considered significant.

RESULTS

Tables I and II list clinical characteristics and risk factors of the 2 groups.

Coronary collateral circulation was more extensive ($p < 0.01$) in the hypertensive group. Eleven of the hypertensive and 55 of the normotensive group patients had class 0 coronary collateral circulation; 7 and 85 patients, respectively, had class I; 26 and 79 patients, respectively, had class II; and 17 and 33 patients, respectively, had class III coronary collateral circulation (Figure 1).

Coronary collateral circulation was more extensive ($p < 0.02$) in patients with right coronary artery disease than in those with left anterior descending disease; 27 of the patients with right coronary artery disease and 39 of the patients with left anterior descending disease had class 0 coronary collateral circulation; 35 and 57 patients, respectively, had class I; 62 and 43 patients, re-

spectively, had class II; and 30 and 20 patients, respectively, had class III coronary collateral circulation (Figure 2).

Left ventricular wall thickness in 13 patients with class III collateral circulation was 1.28 ± 0.09 cm; in 19 class II patients it was 1.28 ± 0.10 cm; in 6 class I patients it was 1.24 ± 0.06 cm; and in class 0 patients it was 1.24 ± 0.11 cm. Patients with class II and III collateral circulation had significantly ($p < 0.001$) greater left ventricular wall thickness than patients with class 0 and I collateral circulation (Figure 3).

Global ejection fraction was $49 \pm 7\%$ in the hypertensive and $53 \pm 10\%$ in the normotensive group ($p < 0.05$).

DISCUSSION

The principle findings of this study were that coronary collateral circulation in hypertensive patients with coronary artery disease was more extensive than in normotensive patients with the same characteristics. Collateral circulation in the hypertensive patients was related to left ventricular wall thickness. These findings of augmented coronary collateral circulation in hypertrophied left ventricles are in agreement with those of previous anatomic studies.^{10,11} These studies showed that the frequency of intracoronary anastomosis was increased and the collaterals were of greater caliber in hypertrophied hearts.

Although anatomic studies suggest that coronary collaterals are increased in left ventricular hypertrophy, physiologic studies by Goldstein et al¹² demonstrated that peripheral coronary pressure was low in patients with aortic stenosis and normal coronary arteries. These results implied that the functional significance of collateral vessels in these patients was minimal. Recently published studies from the same laboratory have shown that dogs with hypertension and left ventricular hypertrophy have larger infarcts than do control dogs.¹³ Furthermore, these results implied that collateral resistance may be increased in animals with left ventricular hyper-

trophy and hypertension. However, Sheel et al¹⁴ showed that collateral resistance in control and hypertrophied hearts was similar in an isolated, blood-perfused cardiac preparation. Other studies showed that the coronary arteries of the pressure overloaded hypertrophied hearts have impaired vasodilator and functional capacity.^{15,16}

In our study the angiographically measured coronary collateral circulation could be the result of (1) enlargement of the collateral arteries, (2) a decrease in coronary resistance, and (3) an increase in the blood pressure difference between the epicardial coronary arteries and the coronary sinus. A practical limitation in our study was that the injection rate of the contrast medium in the contralateral artery could not be maintained at a constant level. Another limitation was that we did not measure the coronary resistance and the blood pressure distally in coronary arteries and in the coronary sinus, and for this reason we do not know exactly the mechanism of increased coronary collateral circulation that hypertensive patients had.

Other investigators have shown that collateral growth occurs in humans and in dogs in response to occlusive vascular diseases.¹⁷ However, in our study the duration and extent of coronary artery disease before cardiac catheterization was about the same in both groups. There was, therefore, no relation between either of them and the extent of coronary collateral circulation. The 2 groups also had the same risk factors and clinical characteristics except that the hypertensive group had right coronary artery disease more often.

The hypertensive patients in our study had less myocardial infarction in their history, despite the increased afterload, and this phenomenon could be explained by the protective effect of the augmented coronary collateral circulation. The more severe angina pectoris and the decreased ejection fraction in these patients could be explained by the existence of increased afterload. How-

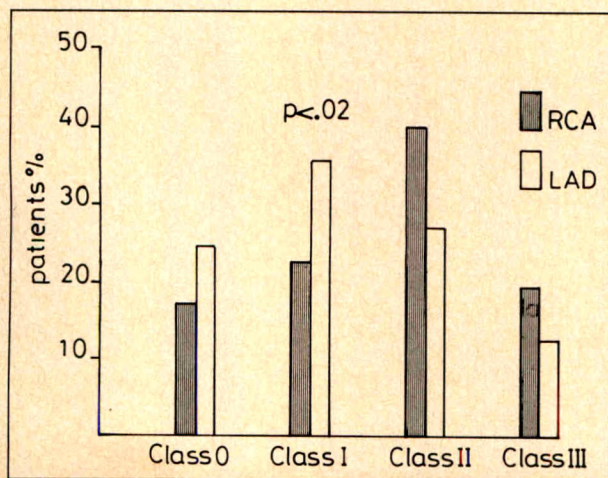


FIGURE 2. Coronary collateral circulation in the right coronary artery (RCA) and left anterior descending (LAD) artery. Collaterals were more extensive in the right coronary artery than in the left anterior descending artery.

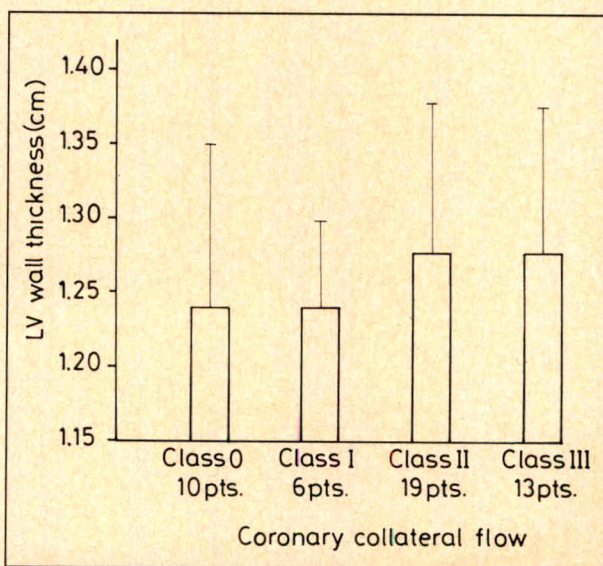


FIGURE 3. Left ventricular (LV) wall thickness in relation to coronary collateral circulation. Class II and III patients had significantly ($p < 0.001$) greater left ventricular wall thickness than class 0 and I patients.

ever, because of the disparity in the size of the groups, these findings are only tentative.

It is not clearly known why left ventricular hypertrophy augments coronary collateral circulation. One could suggest that hypertrophy may be associated with increased growth of intracoronary collateral vasculature, the stimulus for which is thought to be related to myocardial ischemia.

The reason for the increased coronary collateral circulation in right coronary artery disease is not known. Coronary vascular resistance is influenced both by factors extrinsic to the arteries, particularly by compressive forces within the myocardium, and by metabolic, neural and humoral factors intrinsic to them, causing changes in the cross-sectional area of coronary resistance vessels. Intramyocardial pressure is determined primarily by ventricular pressure throughout the cardiac cycle.¹⁸⁻²⁰ Because compressive forces exerted by the right ventricle are ordinarily far less than those of the left ventricle, perfusion of the right ventricle is not interrupted during systole. However, knowing these hydraulic differences, one could suggest that the coronary collateral circulation could be greater for the right coronary artery, even if the same quantity of collateral vessels existed in the left coronary artery.

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Results of Intracoronary Stents for Management of Coronary Dissection After Balloon Angioplasty

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Dissections after coronary balloon angioplasty are risk factors for acute or subacute vessel closures. Intracoronary stenting was developed to avoid these complications by pressing the intimal and medial flaps against the vessel wall, thus reducing the risk of acute thrombosis. A total of 22 stents were implanted into the coronary arteries of 15 patients with dissections after balloon angioplasty causing angina pectoris or ischemic electrocardiographic changes. Stent delivery was successful in all cases. In 1 patient acute stent thrombosis was documented and treated successfully by thrombolytic therapy. Another patient underwent coronary artery bypass surgery 24 hours later because of persisting angina. Angiograms after 24 hours documented vessel patency in the remaining 14 patients. Late control angiograms after 4 to 6 months were obtained in 12 of 14 patients. Vessel patency without significant restenosis was observed in 8 patients, restenosis in 3 and reocclusion in 1 patient. All 3 patients with multiple stent implantation had restenosis ($n = 2$) or reocclusion ($n = 1$), compared with 1 patient with single stent implantation.

Thus, intracoronary stenting appears to be a secure and effective method of handling bailout situations caused by dissection after balloon angioplasty, with good long-term results when only a single stent is implanted.

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Coronary balloon angioplasty is an effective treatment for patients with coronary artery disease.¹⁻⁵ Nevertheless, acute complications such as dissections, vessel ruptures or acute thrombosis, and late restenosis are still serious side effects and limitations.⁵⁻⁹ Coronary stents are designed to handle these acute complications and to lower the rate of late restenosis. Two types of stents—self-expandable and balloon-expandable—are used in clinical practice.¹⁰⁻¹⁵ We report the implantation of balloon-expandable stents in human coronary arteries with symptomatic dissections after balloon angioplasty.

METHODS

The stent: The balloon-expandable stent, designed by Palmaz and Schatz^{11,12} (Figure 1), consists of 2 tubular stainless steel meshes connected with a single bridge (length 1.4 cm and diameter 1.67 mm before expansion). After balloon inflation the stent expands up to the maximum balloon diameter and is pressed against the vessel wall. Low inflation pressures are sufficient to accomplish complete stent expansion, minimizing the risk of balloon rupture.^{11,12}

Patients: Under bailout conditions, intracoronary stenting was attempted in 15 patients (2 women and 13 men, aged 54 to 69 years) who had dissections after balloon angioplasty accompanied by angina pectoris and ischemic electrocardiographic changes. Anamnestic, clinical and procedure-related data are listed in Tables I and II. All patients gave informed consent for balloon angioplasty procedures and for stent implantation in cases of restenosis or bailout situations.

Procedure: Premedication consisted of 500 mg aspirin, 10 mg of nifedipine 3 times daily, and 75 mg of dipyridamole twice daily starting 2 days before the procedure. In the catheterization laboratory all patients received 100 ml/hour of dextran before the procedure, an intravenous bolus injection of 10,000 IU of heparin, and continuous infusion of 1,200 IU/hour of heparin, 0.5 mg/hour of nifedipine and 3 mg/hour of nitroglycerin. Coronary angiograms of the left and right coronary arteries were recorded in several projections to document the target lesion and the collateral supply. Angioplasty of the target lesion was then performed using 9Fr Judkins guiding catheters (Medtronic) and balloon catheters (ACS™, ACX™ and Hydro-Cross™, Edwards) ranging from 2.0 to 3.5 mm in diameter. The maximal inflation pressure was 8 atm, and the maximal inflation period ranged from 20 to 60 seconds. A total of 1 to 3 inflations were performed. Before control angi-

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TABLE I Anamnestic and Clinical Data of the 15 Patients with Symptomatic Coronary Dissections After Balloon Angioplasty Treated with Intracoronary Stenting

Pt. No.	Age (yr) & Sex	Previous		Angina Pectoris	Risk Factors
		MI	PTCA		
1	69 M	PMI 89	—	CCS III	Ila, S
2	63 M	—	LAD 88	CCS II	Ila, H, A
3	67 M	AMI 88	RIM 88	CCS III	H, S
4	54 M	—	—	CCS II	DII, A, S
5	57 M	AMI 88	—	CCS III	H, S
6	68 F	—	—	CCS II	—
7	58 M	AMI 88	LAD 87	CCS III	—
8	67 M	IMI 88	RCA 87	CCS III	Ila
9	64 M	IMI 88	RCA 88	CCS II	Ila, S
10	63 M	AMI 88	LAD 88	CCS III	N
11	58 M	AMI 88	LAD 88	CCS III	Ila, S
12	65 M	PMI 89	—	CCS III	—
13	69 F	—	—	CCS III	Ila, A
14	60 M	—	LAD 89	CCS II	IV, S, A
15	59 M	—	LAD 88	CCS II	Ila, S

A = adiposis; AMI = anterior myocardial infarction; CCS = classification of angina pectoris according to the Canadian Cardiovascular Society; DII = type II diabetes mellitus; H = hypertension; IMI = inferior myocardial infarction; LAD = left anterior descending artery; S = smoking; PMI = posterior myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; RIM = intermediate branch; RCA = right coronary artery; Ila = type Ila hyperlipoproteinemia.

ography, 0.2 mg of nitroglycerin and 3,000 IU of heparin were injected intracoronarily. If the control angiograms documented a dissection membrane at the site of dilatation and if, in a bailout situation, the patient reported angina and ischemic electrocardiographic changes were present (Table II), we proceeded to implant a Palmaz-Schatz stent. The stent was mounted between the radiopaque markers of a 3.0-mm balloon catheter (USCI™), which are helpful in exact stent localization as the mesh is not radiopaque. The length of the balloon is 2.5 cm and prevents vessel damage by covering the ends of the stent (Figure 1). The balloon with the mounted stent was then inserted to the dissect-

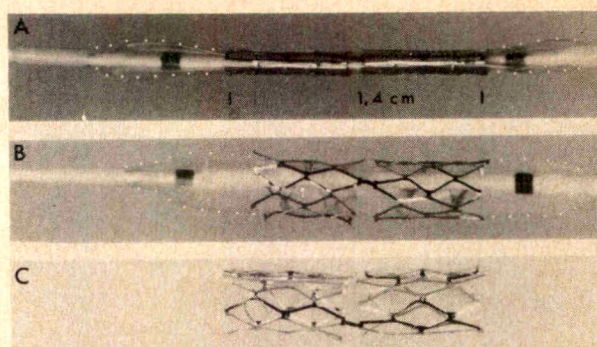


FIGURE 1. The Palmaz-Schatz stent, a balloon-expandable stent for intracoronary implantation. **A**, before balloon inflation; **B**, after balloon inflation; **C**, after withdrawal of the balloon catheter. White dots represent the shape of the balloon.

ed lesion and inflated to a pressure of 12 atm for 5 to 10 seconds using the long wire technique. Another angioplasty was performed within the stent in 10 of 15 patients using a 3.5-mm angioplasty catheter to achieve some overdilatation of the stented vessel segment and good fixation of the stent to the vessel wall. Finally, control angiograms were recorded in different oblique projections.

Follow-up: To assess short-term vessel patency, additional angiograms were obtained 24 hours after stent implantation. All patients received continuous medication consisting of 10 mg of nifedipine 3 times daily, 75 mg of dipyridamole twice daily, and 500 mg of aspirin per day until late control angiograms were recorded 4 to 6 months later. The last 12 patients also received coumarin at Quick levels of <30% for 3 months, based on the results on subacute thrombosis.

Quantitative coronary angiography: The minimal coronary stenosis diameter was evaluated quantitatively on the basis of 2 orthogonal views that provided optimal illustration of the target lesion; these views were also

TABLE II Procedure-Related Data of the 15 Patients with Symptomatic Coronary Dissections After Balloon Angioplasty Treated with Intracoronary Stenting

Pt. No.	Target Lesion	Collaterals	After PTCA + Dissection		Stents	After Stenting		Complications
			Angina	ECG Changes		Angina	ECG Changes	
1	RCA S	++	++	ST 0.2 mV	1	+	—	—
2	LAD S	++	+	ST 0.1 mV	1	—	ST 0.1 mV	—
3	RIM S	++	+++	ST 0.3 mV	1	+	ST 0.1 mV	—
4	LAD S	++	+++	ST 0.4 mV	1	++	ST 0.1 mV	CABG
5	LAD S	+++	++	ST 0.3 mV	3	—	—	—
6	LAD S	++	++	ST 0.2 mV	1	—	—	—
7	LAD S	++	++	ST 0.2 mV	1	—	ST 0.1 mV	—
8	RCA O	+++	+++	ST 0.4 mV	4	—	ST 0.1 mV	—
9	RCA S	++	++	ST 0.3 mV	3	+	—	—
10	LAD S	++	++	ST 0.2 mV	1	—	—	—
11	LAD S	++	++	ST 0.2 mV	1	—	ST 0.1 mV	Ging. bleed.
12	RCA S	+	+++	ST 0.2 mV	1	+	—	GI bleeding
13	LAD S	+	+	ST 0.2 mV	1	—	—	Thrombus, CPK
14	LAD S	++	++	ST 0.1 mV	1	—	—	—
15	LAD S	++	++	ST 0.2 mV	1	—	—	AVF

AVF = arteriovenous fistula; CABG = coronary artery bypass surgery; CPK = creatine phosphokinase rise; ECG = electrocardiographic; GI = gastrointestinal; Ging. bleed. = gingiva bleeding; LAD = left anterior descending artery; O = occlusion; PTCA = percutaneous transluminal coronary angioplasty; RCA = right coronary artery; RIM = intermediate branch; S = stenosis; ST = ST-segment changes; angina: —=no; +=mild; ++=moderate; +++=severe; collaterals: degree of collateral support, judged from the angiogram +=less, ++=moderate, +++=marked.

used to evaluate short- and long-term vessel patency. We calculated the absolute and relative minimal stenosis diameters according to the assumptions of Brown et al¹⁶ using the guiding catheter as a reference. After angioplasty, 2 minimal luminal diameters were determined, 1 with and 1 without respect to the dissection membrane (Figure 2). Restenosis was defined as >50% reduction in diameter or >50% loss of the initial result.

Statistical analysis: Results are expressed as mean \pm 1 standard deviation and the parametric Wilcoxon signed rank test was used to test for significant differences. A p value <0.05 was considered significant.

RESULTS

The intracoronary stenting procedure was successfully performed in all patients in whom symptomatic coronary dissections occurred after balloon angioplasty causing a marked improvement in anginal symptoms and ischemic electrocardiographic changes (Table II). Acute thrombosis immediately after implantation was observed as the only procedure-related problem in a patient with a stenosis of the left anterior descending artery and clinical symptoms of unstable angina (Figure 3). The angiograms recorded after stent implantation documented contrast medium filling defects within the stented vessel segment, which were interpreted as a thrombus and treated by intracoronary injection of 300,000 IU of urokinase and the additional intravenous infusion of 1.5 million IU of urokinase for 30 minutes. Although asymptomatic, this patient developed a maximal increase in creatine phosphokinase of 400 IU/liter, and the control angiogram after 24 hours documented vessel patency without any persisting filling defects. The result after 4 months was satisfactory without significant residual stenosis.

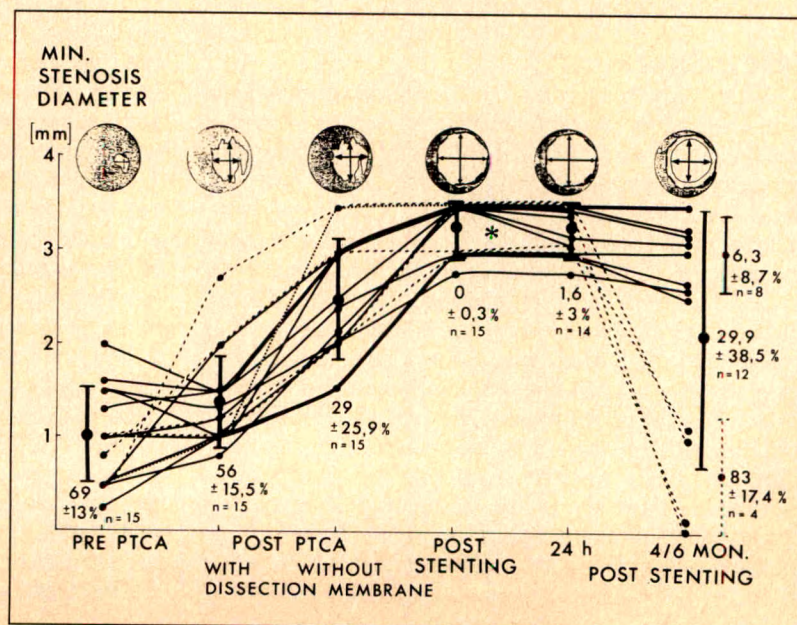
Figure 2 shows individual and mean values of the minimal stenosis diameter for all patients, documenting a marked increase in luminal diameter after stent im-

plantation compared with the results after balloon angioplasty. The relation between the maximal inflated balloon size and the minimal residual stenosis diameter after balloon angioplasty indicates a mean recoil of $\geq 0.7 \pm 0.5$ mm (28.5%), which was not measured after stent implantation. Control angiograms were obtained 24 hours after stent implantation in 14 of 15 patients, documenting continuous satisfactory results. One patient was sent to bypass surgery the day after stent implantation because of persisting angina pectoris but without significant creatine phosphokinase or electrocardiographic changes (Figures 2 and 4). In this patient there was a stenosis of the left anterior descending artery, and the guide wire could not be placed in the distal portion of this artery but instead in the adjacent diagonal branch. After balloon angioplasty there was a long dissection that altered blood flow to the distal portion of the left anterior descending artery even after successful stent delivery.

Currently, 12 of 14 remaining patients have had late follow-up angiograms 4 to 6 months after stent implantation. Significant restenosis was documented in 3 patients, and reocclusion in 1 patient, in whom recanalization of a completely occluded right coronary artery was performed (Figure 2). No significant restenosis was documented in 8 patients. Retrospective analysis of these late follow-up results revealed that all the patients (3 of 15) with multiple stent implantation had restenosis or reocclusion compared with only 1 patient with single stent implantation. Long-term vessel patency was documented in 8 of 9 controlled patients with single stent implantation.

All patients received the intended long-term follow-up medication, especially those who received coumarin therapy with documented Quick levels of <30%. Long-term vessel patency was documented in 2 of 3 patients without and in 6 of 9 patients with coumarin medication. Bleeding complications were observed in 2 pa-

FIGURE 2. Results of minimal (min.) stenosis diameter in 15 patients with symptomatic coronary dissections after percutaneous transluminal coronary angioplasty (PTCA). Individual results and mean \pm 1 standard deviation are illustrated. Two minimal obstructive diameters were measured after PTCA, 1 with and 1 without respect to the dissection membrane. Fourteen patients had short-term follow-up control angiograms 24 hours after stent implantation, 1 patient (*, closed dashed line) underwent coronary bypass surgery the day after angiography. Long-term follow-up angiograms were recorded in 12 of 14 remaining patients after 4 to 6 months (mon.). Patients with late restenosis or reocclusion are illustrated by long dashed lines.



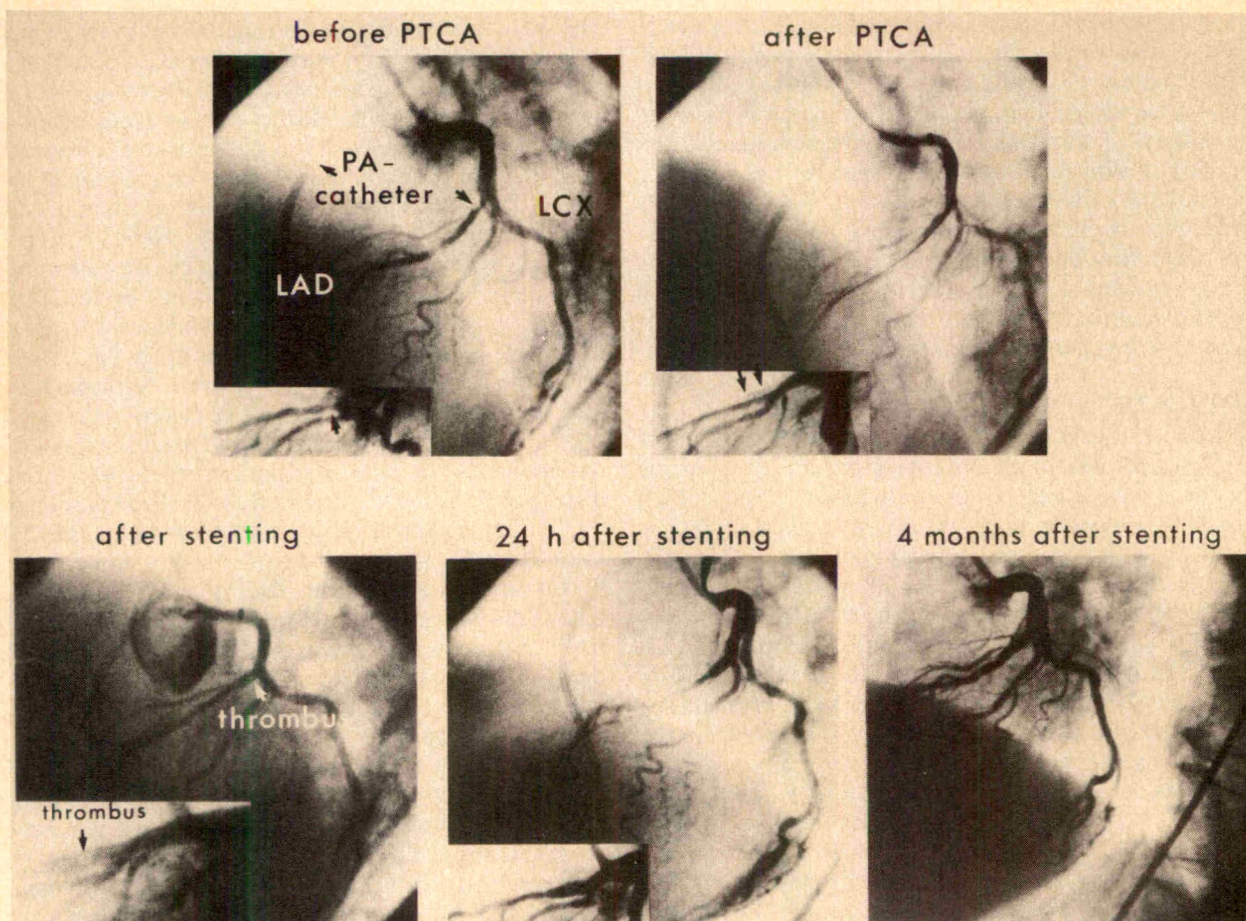


FIGURE 3. Angiograms of a patient with unstable angina with a proximal stenosis of the left anterior descending artery (LAD). After percutaneous transluminal coronary angioplasty (PTCA), a dissection membrane was documented, which was successfully pressed against the vessel wall after stent implantation. Nevertheless, the angiogram shows a contrast medium filling defect within the stented vessel segment, which was interpreted as acute thrombus formation, and was successfully treated by thrombolysis with excellent short- and long-term vessel patency. LCX = left circumflex artery; PA = pulmonary artery.

tients, 1 developing an arteriovenous aneurysm and requiring blood transfusion, the other reporting slight gingiva bleeding during coumarin therapy.

DISCUSSION

This study constitutes our first clinical experience with the balloon-expandable Palmaz-Schatz stent during bailout situations in patients with dissections after coronary balloon angioplasty causing angina and ischemic electrocardiographic changes. Coronary dissections after balloon angioplasty are regarded as a possible reason for acute complications including vessel closure.^{9,17,18} Vessel wall irregularities such as intimal and medial flaps are frequently observed after balloon angioplasty and may induce blood flow alterations and promote thrombus formation. Previous investigations elucidated the relation between the extent of the dissection and the rate of acute complications and restenosis.^{4,9} Coronary stents were designed to press these intimal and medial flaps against the vessel wall to reduce the risk of blood flow alterations and acute thrombus formation resulting in an acute vessel closure, which occurs in 1.1 to 8% of native angioplasty procedures.^{4,5,9,19,20}

Subsequent emergency coronary bypass surgery is requested in 1 to 7%.^{5,19,21,22}

The Palmaz-Schatz stent can be distinguished methodologically from self-expandable stents.^{10,23} This device has been successfully implanted into coronary arteries of patients with coronary artery disease.¹⁵ Acute complications are reported to be rare compared with balloon angioplasty.

Acute thrombosis immediately after stent implantation was the only major stent-related procedural problem, occurring in 1 patient with unstable angina pectoris. It was successfully treated by thrombolysis with an excellent long-term angiographic result, although an increase in creatine phosphokinase levels occurred. Contrary to the previously described antithrombotic purpose of the stent by wrapping vessel wall irregularities, acute thrombosis may be actually promoted by the thrombophilia of the stent itself in conjunction with the condition of unstable angina and the thrombogenic effect of the vessel wall damage after balloon angioplasty.

In 14 of 15 dissections, the intimal and medial flaps were successfully pressed against the vessel wall. In 1 patient the stent implantation was successful but the

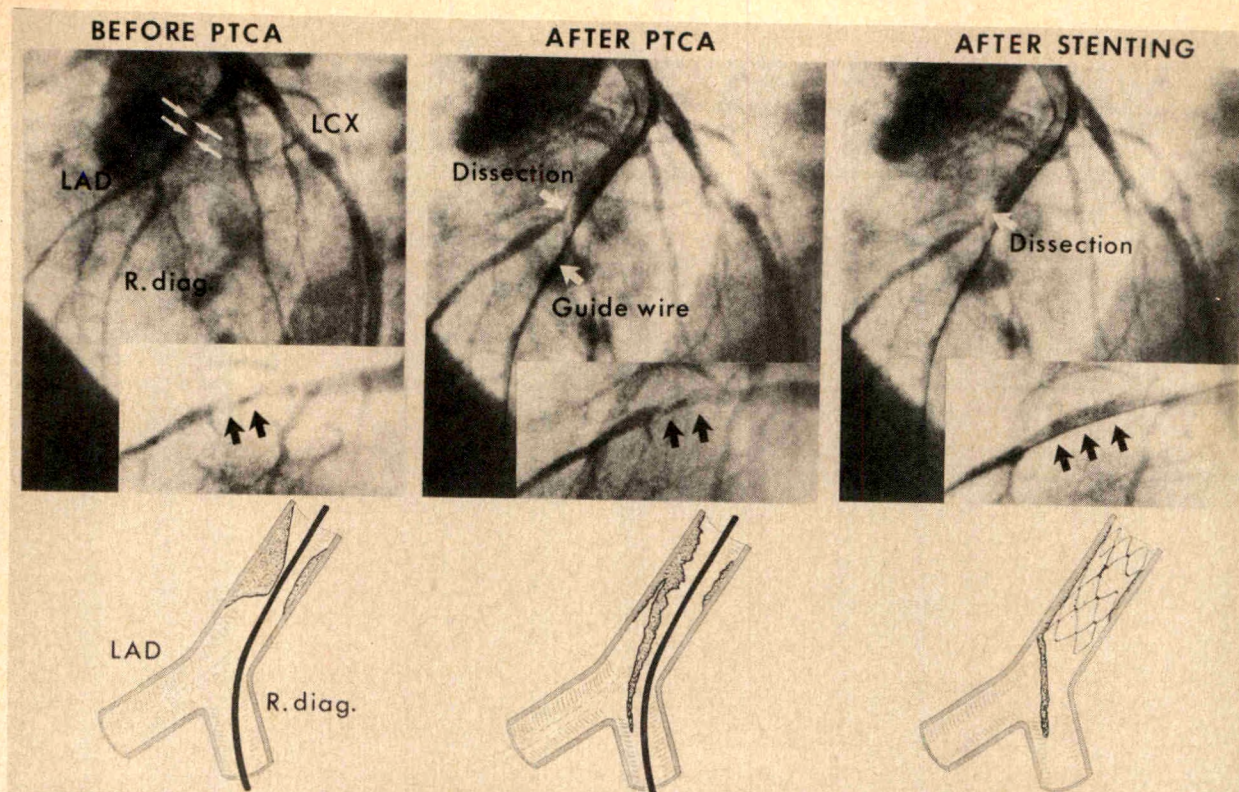


FIGURE 4. Angiograms of a patient with extended coronary dissection in the left anterior descending artery (LAD) after percutaneous transluminal coronary angioplasty (PTCA), which persisted after stent implantation causing repeated episodes of ischemia. The illustrations below should clarify the mechanisms responsible for this unsatisfactory outcome (for explanation see text). LCX = left circumflex artery; R. diag. = diagonal branch.

distal membrane dissection still persisted. In retrospect, this result seems to be related to the angioplasty procedure itself, since it was not possible to position the guide wire correctly in the distal part of the left anterior descending artery. There was consequently no real improvement after stent implantation, which was performed because of severe angina. The patient was sent to elective coronary bypass surgery the next day because of persisting angina. This example emphasizes the importance of correct positioning of the guide wire in the distal part of the target vessel. Long wire or "mono-rail™" techniques should be used to prevent wire displacement while exchanging balloon catheters for stent delivery, especially in the presence of dissections. In comparison, the rate of success for coronary balloon angioplasty is reported to be about 90%.^{2-5,17,22}

Bleeding complications occurred in 2 patients, one of whom required blood transfusions. The complete anticoagulation regimen of coumarin, aspirin and dipyridamole potentially promotes these complications.

Quantitative analysis of the minimal stenosis diameters before and after balloon angioplasty as related to the inflated balloon sizes showed that elastic recoil forces induced a mean residual stenosis of 28.5%. Intracoronary stenting inhibited recoil forces in addition to being a successful treatment for coronary dissections. Similar results have been reported by Puel et al.²³

Long-term follow-up angiograms demonstrated 1 subacute vessel closure, 3 restenoses within the stented

vessel segment, and vessel patency in 8 patients after 4 to 6 months. All patients with multiple stent implantation had late restenosis or reocclusion compared with only 1 patient who received a single stent. The addition of coumarin to the long-term medication had no effect on vessel patency in this limited number of patients.

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Reduction in the Frequency of Ventricular Late Potentials After Acute Myocardial Infarction by Early Thrombolytic Therapy

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Ventricular late potentials are strong predictors of arrhythmic events after acute myocardial infarction (AMI). To assess the effect of intravenous thrombolysis on the incidence of ventricular late potentials, 223 consecutive patients surviving a first AMI were included in the present study: 59 patients (53 men, 6 women, mean age \pm standard deviation 55 ± 10 years) received intravenous recombinant tissue-type plasminogen activator (100 mg over 3 hours, group A) and 164 patients (123 men, 41 women, mean age 61 ± 11 years) received conventional medical treatment (group B). A time-domain signal-averaged electrocardiogram and a high-resolution beat-to-beat recording (gain 10^6 , filters 100 to 300 Hz) were performed at 10 ± 3 days after AMI. There was no difference between group A and B patients in terms of AMI location (anterior in 28 of 59 vs 80 of 164, difference not significant [NS]), mean left ventricular ejection fraction (55 ± 10 vs $55 \pm 13\%$, NS), or presence of heart failure (New York Heart Association class III or IV in 12 of 59 vs 40 of 164, NS). The incidence of ventricular late potentials was 10% (6 of 59) in group A and 24% (39 of 164) in group B ($p < 0.05$). Among the 146 patients who underwent coronary arteriography, the incidence of ventricular late potentials was 13% (10 of 80) in patients with a patent infarct-related artery and 26% (17 of 66) in patients with an occluded infarct-related artery ($p < 0.05$). No relation was found between the presence of ventricular late potentials and the presence of nonsustained ventricular tachycardia as detected by 24-hour Holter monitoring. In conclusion, intravenous thrombolysis with recombinant tissue-type plasminogen activator reduces the incidence of ventricular late potentials in survivors of a first AMI; this reduced frequency is not related to global left ventricular function and appears to be related to the patency of the infarct-related artery (induced

by a thrombolytic agent or occurring spontaneously). Further prospective studies are needed to assess the prognostic significance of this finding.

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During the first year after acute myocardial infarction (AMI), mortality varies from 7 to 11%; half of these deaths are sudden and presumably due to malignant ventricular arrhythmias.¹⁻³ In recent years, high-gain electrocardiography and signal-averaging techniques have allowed the noninvasive detection of ventricular late potentials in patients with documented sustained ventricular tachyarrhythmias.⁴⁻⁷ Ventricular late potentials are thought to represent delayed activation of some areas of the myocardium and their presence in patients after AMI is associated with an increased risk of ventricular tachycardia and sudden death.⁸⁻¹⁴ Thrombolytic agents are being used with increasing frequency in the treatment of AMI, and have been found to reduce mortality after AMI.^{15,16} This favorable effect may be related to preservation of left ventricular function but may also reflect reduction in electrical instability, since ventricular tachycardia has been shown to be inducible less often in patients who have received thrombolytic therapy.^{17,18} The purposes of this study were: (1) to assess prospectively, in a large group of unselected patients surviving a first AMI, the effect of thrombolysis with recombinant tissue-type plasminogen activator (rt-PA) on the incidence of ventricular late potentials after AMI; and (2) to determine the influence of infarct-related artery patency on the incidence of ventricular late potentials after AMI.

METHODS

Patients: Between January 1987 and November 1988, 325 patients were admitted with AMI. To avoid misinterpretation of the high-gain recordings, patients with previous coronary artery bypass grafting or documented AMI ($n = 67$) and patients with complete bundle branch block ($n = 21$) were excluded, as well as patients who died during AMI ($n = 14$). Fifty-nine patients (26%) received an intravenous infusion of 100 mg of rt-PA over 3 hours (group A); the decision to administer thrombolytic therapy was made by the attending physician and was based on the presence of typical prolonged chest pain with ST-segment elevation on the

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electrocardiogram (1 mm in the limb leads, 2 mm in the precordial leads). Rt-PA was always administered within 4 hours after the onset of symptoms. Exclusion criteria were: age >70 years, previous resuscitation, active bleeding, recent stroke or surgery. Conventional therapy was administered to 164 patients (76% of the study group) who did not qualify for thrombolytic therapy (group B).

The final diagnosis of AMI was based on the presence of typical prolonged chest pain, accompanied by an abnormal elevation of total creatine kinase with an MB fraction of $\geq 10\%$, and by evolving electrocardiographic changes consistent with Q-wave or non-Q-wave AMI. All patients had a complete physical examination, serial 12-lead electrocardiograms and cardiac enzyme determinations, continuous on-line electrocardiographic monitoring during at least the first 36 hours after admission, a signal-averaged electrocardiogram and a high-resolution beat-to-beat recording. In addition, 146 of 223 survivors (65%) underwent coronary arteriography at a mean of 5 ± 3 days (range 1 to 17) after admission, 98 of 223 (44%) had radionuclide ventriculography, 151 of 223 (68%) underwent low-level exercise stress testing and 194 of 223 (87%) had 24-hour Holter monitoring during the in-hospital phase.

Time-domain signal-averaged electrocardiogram:

A time-domain signal-averaged electrocardiogram was performed in all patients at 10 ± 3 days (range 7 to 13) after admission. Recordings were performed using the signal averager extensively used by our group and previously described.¹⁰ Band-pass filters are set at 100 and 300 Hz (12 dB/octave), the peak of R wave is used as trigger (jitter <0.5 ms) and bipolar chest leads (between V_2 and V_4 , V_4 and V_6) are used. The averaging process is performed on 32 consecutive beats in order to reduce the baseline noise to $0.3 \pm 0.2 \mu V$. The recording ($2 \mu V/cm$) is plotted on paper (paper speed of 1,000 mm/s) together with a reference electrocardiogram ($200 \mu V/cm$). Quantitative analysis includes: (1) total filtered QRS duration (in ms); and (2) interval between the end of total QRS complex and the point (determined retrogradely) when QRS voltage falls below $40 \mu V$ (I-40, in ms). QRS onset and offset are manually determined and all tracings are interpreted by 2 different investigators without knowledge of the patient's group or angiographic status. Ventricular late potentials were considered to be present if the 2 following criteria were met: (1) total filtered QRS duration >118 ms; and (2) I-40 >45 ms (maximal value for normal subjects in our laboratory).

High-resolution beat-to-beat recording: To detect dynamic changes of late potentials, we developed a 3-channel high-resolution electrocardiogram¹⁹ which was used together with the time-domain signal averager in all patients. The input signal is fed through a preamplifier with a gain of 1,000; the band-pass filtering is made by filters of the Sallen-Key type: the high-pass filter (-10 dB in the first octave, -20 dB in the second octave and -35 dB in the third octave) is adjustable between 10 and 150 Hz in 10-Hz step increments; the low-pass filter (-20 dB in the first octave and -50 dB

in the second octave) is adjustable between 100 and 1,000 Hz in 100-Hz step increments. A final amplifier provides the necessary gain to obtain a 1 to $10 \mu V/cm$ tracing on the recorder (Siemens Mingograph 82). No averaging process is used; in clinical conditions, noise level is 1 to $2 \mu V$ peak to peak. One channel is used for the reference tracing ($0.5 mV/cm$), and 2 channels for high-gain recordings at different high-pass filter settings. The same chest leads as with the signal averager are used. Recordings are performed at the bedside, in a nonshielded room, and no premedication is required. For each patient, a minimum of 100 consecutive beats is recorded in each lead; because noise varies with respiratory movements, analysis is performed during periods of least noise level. Noise should be $<3 \mu V$ peak to peak to allow quantitative analysis, and a minimum of 5 interpretable sequences are analyzed by 2 different cardiologists, in a blinded manner. The following measurements are obtained: (1) total filtered QRS duration (in ms); (2) interval between the end of total QRS and the point (determined retrogradely) when QRS voltage falls below $40 \mu V$ (I-40, in ms); and (3) QRS voltage (peak to peak) 40 ms before the end of total QRS complex (V40, in μV). Ventricular late potentials were considered present if the following criteria were met at 100 to 300 Hz: (1) total QRS duration >100 ms; and (2) I-40 >30 ms; or (3) V40 < $40 \mu V$ (maximal value for normal subjects in our laboratory).

Definitions: Ventricular tachycardia is ≥ 3 consecutive complexes of ventricular origin at a rate ≥ 100 beats/min; sustained is duration ≥ 30 seconds or requiring active termination; nonsustained is duration ≤ 30 seconds and terminated spontaneously; sudden death is death occurring within 1 hour of symptoms in a clinically stable patient or unexpected death occurring during sleep; cardiac death is death from intractable heart failure; noncardiac death is death definitely due to a noncardiac cause; and 1-, 2- or 3-vessel disease is the presence of >70% stenosis in 1, 2 or 3 major coronary arteries.

Statistical analysis: Values are expressed as mean \pm standard deviation. Differences in normally distributed continuous variables between 2 groups were compared using Student's *t* test for unpaired data. Statistical analysis of discrete variables was performed using the chi-square test. A *p* value <0.05 was considered statistically significant.

RESULTS

Clinical data: The characteristics of the study population are listed in Table I. Patients who received thrombolytic therapy (group A) were significantly younger, had non-Q-wave AMI less often and more frequently exhibited coronary artery stenosis <70% at angiography. However, there were no differences between the 2 groups with respect to the site of AMI, size of the infarct, incidence of clinical signs of heart failure or global left ventricular ejection fraction.

Incidence of ventricular late potentials: The incidence of ventricular late potentials was 10% (6 of 59) in patients who received thrombolytic therapy (group A)

and 24% (39 of 164) in patients who received conventional medical therapy (group B) ($p < 0.05$). Examples of normal and abnormal recordings are presented in Figures 1 and 2. Concordant results between time-domain signal-averaging and high-resolution beat-to-beat recording were observed in 93% of the patients (207 of 223). Late potentials were detectable by signal-averaging in 6 of 6 group A patients and in 34 of 39 group B patients; late potentials were detectable by high-resolution beat-to-beat electrocardiography in 4 of 6 group A patients and in 30 of 39 group B patients (Figure 3). Thus, in 2 of 6 group A patients and in 9 of 39 group B patients, late potentials were detectable only by time-domain signal-averaging techniques, and in 5 of 39 group B patients, late potentials were detectable only by high-resolution beat-to-beat techniques. Despite the significant difference in the incidence of late potentials between groups A and B, there was no difference in the quantitative high-gain parameters: total filtered QRS duration — 109 ± 10 ms in group A and 108 ± 13 ms in group B using time-domain signal-averaging (difference not significant [NS]); 93 ± 9 ms in group A and 92 ± 10 ms in group B using the high-resolution beat-to-beat technique (NS); I-40 — 30 ± 13 ms in group A and 42 ± 14 ms in group B using time-domain signal-averaging (NS); 25 ± 9 ms in group A and 26 ± 11 ms in group B using the high-resolution beat-to-beat technique (NS).

Relation between presence of late potentials and left ventricular ejection fraction: Mean left ventricular ejection fraction was not statistically different between patients with ($53 \pm 12\%$) and without ($57 \pm 12\%$, $p = 0.08$) late potentials.

TABLE I Characteristics of Patients With and Without Thrombolysis for Acute Myocardial Infarction

	Group A— Thrombolysis (n = 59)	Group B— No Thrombolysis (n = 164)
Mean age (\pm SD) (yr)	55 ± 10	$61 \pm 11^*$
Men/women	53/6	123/41
Peak total CK level (U/liter)	$2,155 \pm 1,616$	$1,465 \pm 1,587$
Peak CK-MB level (U/liter)	214 ± 146	150 ± 136
Anterior MI (%)	28/59 (47)	80/164 (49)
Non-Q-wave MI (%)	4/59 (7)	30/164 (18)*
Heart failure NYHA III–IV (%)	12/59 (20)	40/164 (24)
Mean LVEF (%)	55 ± 10	55 ± 13
Coronary arteries		
No significant stenosis (%)	7/43 (16)	3/103 (3)*
1-vessel disease (%)	18/43 (42)	49/103 (48)
2-vessel disease (%)	13/43 (30)	23/103 (22)
3-vessel disease (%)	5/43 (12)	28/103 (27)
Sustained VT/VF (initial phase) (%)	4/59 (7)	12/164 (7)

* $p < 0.05$ versus group A values.

CK = creatine kinase; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NYHA = New York Heart Association; SD = standard deviation; VT/VF = ventricular tachycardia/ventricular fibrillation.

Relation between presence of late potentials and infarct-related artery patency: Coronary arteriography was performed in 146 patients during the in-hospital phase of AMI (43 of 59 group A patients and 103 of 164 group B patients). A patent infarct-related artery was present in 35 of 43 group A patients (81%), and in 45 of 103 group B patients (44%) ($p < 0.001$). No significant differences were found in clinical, angiographic and electrocardiographic characteristics between patients with and without a patent infarct-related artery.

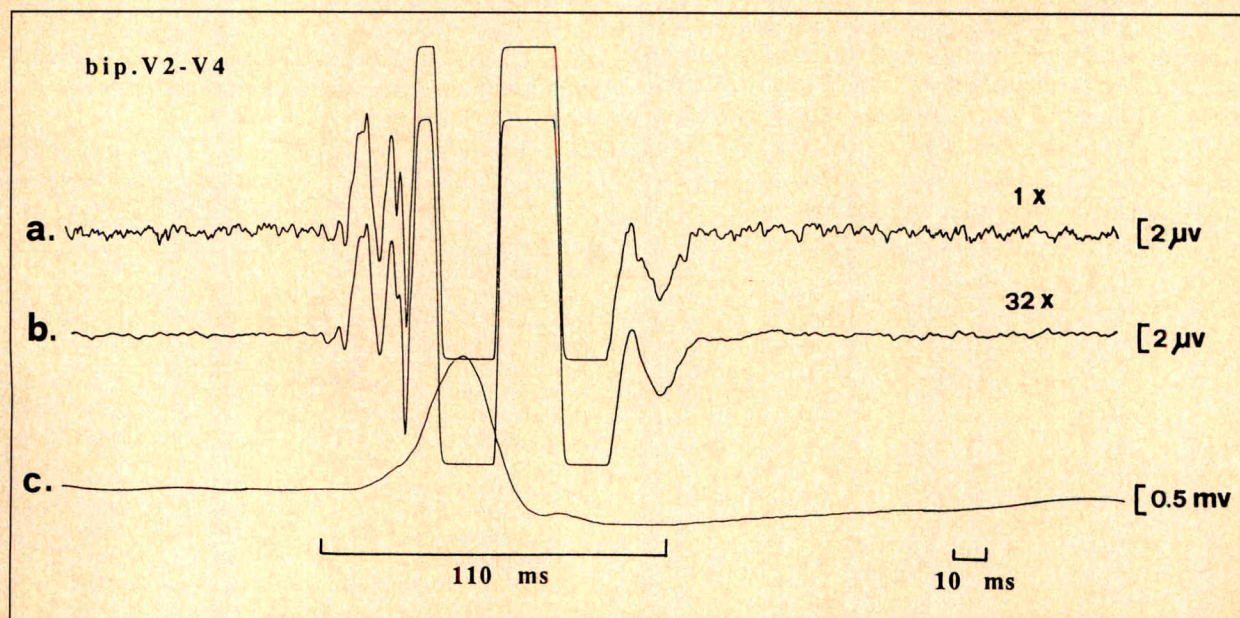


FIGURE 1. High-gain recording in a 71-year-old patient with acute anterior myocardial infarction and successful reperfusion after recombinant tissue-type plasminogen activator administration (group A). Bipolar chest lead between V_2 and V_4 ; band-pass filters of 100 and 300 Hz; recording performed 11 days after myocardial infarction. *a.*, high-resolution beat-to-beat recording (1 \times , 2 μ V/cm), and noise level 1.5 μ V peak to peak; *b.*, time-domain signal-averaged recording (2 μ V/cm) obtained by the averaging of 32 consecutive cardiac cycles (32 \times), and noise level <0.3 μ V; *c.*, reference electrocardiogram (0.5 mV/cm). The total filtered QRS duration is 110 ms, and no ventricular late potentials are present in the terminal portion of the QRS complex.

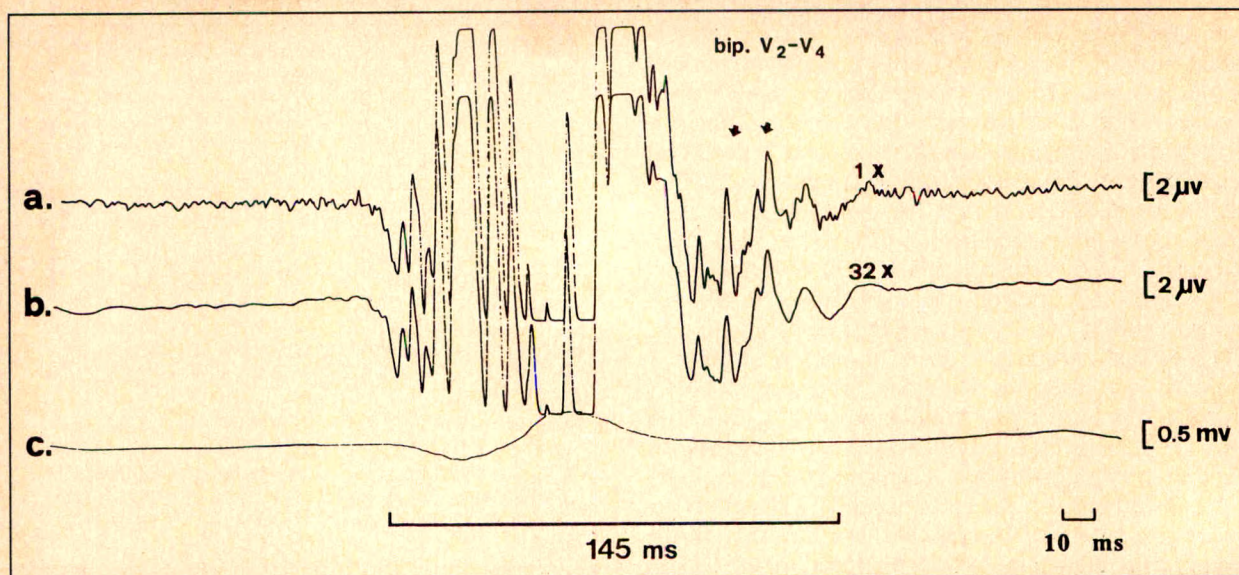


FIGURE 2. High-gain recording in a 67-year-old patient with acute inferior myocardial infarction who did not receive thrombolytic therapy (group B). Bipolar chest lead between V₂ and V₄; band-pass filters of 100 and 300 Hz; recording performed 10 days after myocardial infarction. *a.*, high-resolution beat-to-beat recording (1×, 2 μV/cm), and noise level 1.2 μV peak-to-peak; *b.*, time-domain signal-averaged recording (32×, 2 μV/cm), and noise level <0.2 μV; *c.*, reference electrocardiogram (0.5 mV/cm). The total filtered QRS duration is 145 ms, and low-amplitude, high-frequency signals (arrows) are present in the terminal portion of the QRS complex. These ventricular late potentials are detected both by time-domain signal-averaging (32×) and by beat-to-beat high-resolution electrocardiography (1×).

(Table II). The incidence of late potentials was 13% (10 of 80) in patients with a patent infarct-related artery (3 of 35 patients with and 7 of 45 patients without thrombolytic therapy) compared with 26% (17 of 66) in patients with an occluded infarct-related artery (1 of 8 patients with and 16 of 58 patients without thrombolytic therapy) ($p < 0.05$).

The total filtered QRS duration with signal-averaging and the I-40 with the high-resolution beat-to-beat technique were significantly longer in patients with an occluded infarct-related artery: total filtered QRS duration — 108 ± 13 ms in patients with a patent in-

farct-related artery and 113 ± 14 ms in patients with an occluded infarct-related artery with time-domain signal-averaging ($p < 0.05$); 93 ± 9 and 96 ± 14 ms, respectively, with the high-resolution beat-to-beat technique (NS); I-40 — 42 ± 14 ms in patients with a patent infarct-related artery and 47 ± 14 ms in patients with an occluded infarct-related artery with time-domain signal-averaging (NS); 22 ± 8 and 26 ± 11 ms,

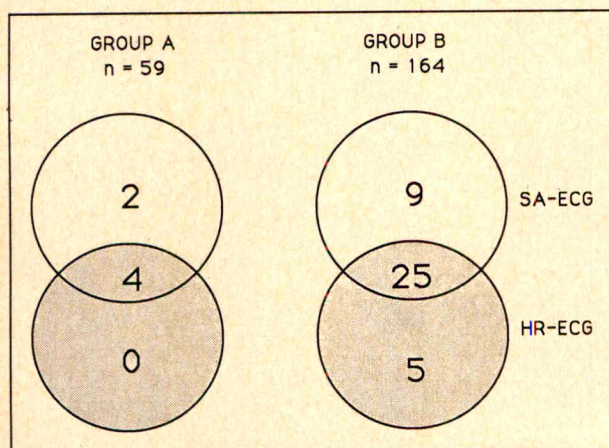


FIGURE 3. Concordance of results between time-domain signal-averaging (SA-ECG) and high-resolution beat-to-beat electrocardiography (HR-ECG) for the noninvasive detection of ventricular late potentials, in patients with thrombolysis ($n = 59$) and in patients with conventional medical treatment ($n = 164$). See text for details.

TABLE II Characteristics of Patients With and Without a Patent Infarct-Related Artery

	Patency of Infarct-Related Artery ($n = 80$)	Occlusion of Infarct-Related Artery ($n = 66$)
Mean age (\pm SD) (yr)	57 ± 10	55 ± 10
Men/women	65/15	54/12
Peak total CK level (U/liter)	$1,597 \pm 1,895$	$1,720 \pm 1,615$
Peak CK-MB level (U/liter)	153 ± 129	181 ± 173
Anterior MI (%)	38/80 (48)	27/66 (41)
Non-Q-wave MI (%)	11/80 (14)	14/66 (21)
Heart failure NYHA III-IV (%)	15/80 (19)	11/66 (17)
Mean LVEF (%)	57 ± 11	54 ± 12
Coronary arteries		
No significant stenosis (%)	10/80 (13)	0/66 (0)
1-vessel disease (%)	35/80 (44)	32/66 (48)
2-vessel disease (%)	19/80 (23)	17/66 (26)
3-vessel disease (%)	16/80 (20)	17/66 (26)
Sustained VT/VF (initial phase) (%)	7/80 (9)	2/66 (3)
Holter data		
Polymorphous VPCs (%)	11/69 (16)	14/55 (25)
Couplets (%)	12/69 (17)	9/55 (16)
Nonsustained VT (%)	5/69 (7)	2/55 (4)

$p < 0.05$ versus group A values.

VPCs = ventricular premature complexes; other abbreviations as in Table I.

respectively, with the high-resolution beat-to-beat technique ($p < 0.05$).

Relation between thrombolytic therapy and results of 24-hour Holter monitoring: A 24-hour Holter recording was performed in 87% of the study group before hospital discharge (194 of 223): 53 of 59 group A patients and 141 of 164 group B patients. There was no difference between patients with and without thrombolytic therapy with respect to the presence of polymorphous ventricular premature complexes (11 of 53 in patients with vs 31 of 141 in patients without thrombolytic therapy, NS), presence of couplets (10 of 53 in patients with vs 26 of 141 in patients without thrombolytic therapy, NS), or presence of runs of nonsustained ventricular tachycardia (3 of 53 in patients with vs 11 of 141 in patients without thrombolytic therapy, NS). Nonsustained episodes of accelerated idioventricular rhythm (rate < 100 beats/min) were observed in 3 of 53 patients with and in 0 of 141 patients without thrombolytic therapy ($p < 0.01$). Similarly, no significant differences were found in the frequency of complex ventricular arrhythmias between patients with and without a patent infarct-related artery (Table II).

Follow-up data: During a mean follow-up of 16 ± 4.5 months, 17 of 223 patients (7.6%) died and 24 of 223 (11%) were lost to follow-up (6 of 59 in group A and 18 of 164 in Group B). Only 1 death occurred in the group of patients who had received thrombolytic therapy: this patient had late potentials at hospital discharge and died suddenly 8 weeks after AMI. In the conventionally treated group 16 deaths were observed ($p < 0.05$ vs group A patients): 8 patients died suddenly, 3 from cardiogenic shock, 3 from noncardiac causes and 2 from unknown causes. Among these 16 patients, 5 had late potentials before hospital discharge and all 5 died suddenly: 3 of 5 had late potentials on time-domain signal-averaging and on the high-resolution beat-to-beat recording, and 2 of 5 had late potentials only on the high-resolution beat-to-beat recording. All patients who died nonsuddenly had normal signal-averaged and high-resolution beat-to-beat recordings. Characteristics of patients who died suddenly during follow-up are listed in Table III. For predicting sudden death, the presence of late potentials had a sensitivity of 67% and a specificity of 80%.

DISCUSSION

Several recent studies have shown that signal-averaged electrocardiography provides important prognostic information in identifying patients at risk of arrhythmic events after AMI.⁹⁻¹⁴ Late potentials are only rarely influenced by drugs and only surgical exclusion of arrhythmogenic tissue has been shown to suppress late potentials.^{5,10,20} Thus, any intervention leading to a suppression of late potentials is expected to reduce the risk of ventricular tachycardia and sudden death in patients after AMI. In the present study, we have shown that thrombolysis reduces the frequency of late potentials from 24 to 10% in a large group of unselected patients presenting with a first AMI. Similar results have recently been published by others in smaller groups of pa-

TABLE III Characteristics of Patients Who Died Suddenly During Follow-Up

	Sudden Death (n = 9)	Alive (n = 182)
Mean age (\pm SD) (years)	$73 \pm 4^*$	60 ± 11
Men/women	6/3	143/39
Anterior MI (%)	5/9 (56)	85/182 (47)
Non-Q-wave MI (%)	0/9 (0)	29/182 (16)
Heart failure NYHA III-IV (%)	7/9 (78)*	36/182 (20)
Mean LVEF (%)	$43 \pm 11^*$	56 ± 12
Sustained VT/VF (initial phase) (%)	3/9 (33)*	10/182 (5)
Thrombolysis (%)	1/9 (11)	44/182 (24)
Ventricular late potentials (%)	6/9 (67)*	31/182 (17)

* $p < 0.01$ versus values while alive.
Abbreviations as in Table I.

tients²¹⁻²³ and may, at least in part, explain the beneficial effect of early thrombolytic therapy on mortality after AMI.^{15,16} In our study, the mortality rate after AMI was significantly lower in patients who had received early thrombolytic therapy compared with patients who had conventional medical therapy (1 of 59 vs 16 of 164, $p < 0.05$). Although the number of deaths and arrhythmic events is too small to allow a definite conclusion, we observed that half of the deaths during follow-up were sudden. Moreover, most patients who died suddenly during follow-up had late potentials before hospital discharge; this observation is in accordance with previous prospective studies in patients after AMI.^{8,14}

The reduced incidence of late potentials produced by rt-PA in our study was independent of global left ventricular function because the mean ejection fraction was similar in group A and B patients. This observation is in accordance with previous studies on electrical stability after thrombolysis for AMI.¹⁷⁻²¹ In our study, as in others,^{21,23} the favorable effect of thrombolytic therapy was related to patency of the infarct-related artery; the exact mechanism by which reperfusion reduces the incidence of late potentials is unclear, but several well-conducted prospective studies have shown that patients with early thrombolysis had improved arrhythmia-free survival and electrical stability.¹⁷ Thrombolytic therapy may reduce ischemia in the border zone of the infarct, may change electrophysiologic properties of surviving cells, may influence the remodeling process after AMI²⁴ or may facilitate focal hemorrhage²⁵. All these effects may suppress slow and inhomogeneous conduction and, thus, late potentials. Although comparable to the results of Gang et al,²² our findings contrast with those of Turitto et al,²⁶ who recently reported that thrombolysis had no effect on the signal-averaged recording. This discrepancy may be explained by (1) a smaller number of patients, (2) a longer delay in Turitto's report between onset of symptoms and thrombolysis, (3) differences in the thrombolytic agent used, and (4) differences in methodology for the detection of late potentials. Théroux et al²⁷ showed that the number of ventricular premature beats per hour was reduced by 50% in patients who received streptokinase, and that this reduction in ventricular premature beats may at least partly explain

the long-term benefit of reperfusion. Our data do not confirm these results, since the number and complexity of ventricular premature beats during Holter monitoring was identical in patients with and without thrombolytic therapy.

Two different techniques were used to detect late potentials in the present study: time-domain signal-averaging and high-resolution beat-to-beat electrocardiography. Signal-averaging is an established method to detect late potentials from the body surface, although some controversies exist regarding optimal filter settings, criteria to define an abnormal recording,²⁸ or optimal recording time after AMI; in this study, we performed signal-averaging just before hospital discharge because several studies have shown dynamic changes during the first week after AMI.^{13,14} The incidence of late potentials in our study was 24% in patients with conventional therapy, a figure that is in the lower range of published data.^{6,14} A similar low rate was found by Gang²² and Turitto,²⁶ and their co-workers, and may be explained by the fact that only patients with a first AMI were included in our study. The high-resolution beat-to-beat technique is a new, experimental method developed to detect late potentials on a beat-to-beat basis.¹⁹ Theoretically, this approach may allow the identification of dynamic changes of late potentials which, by definition, are eliminated by time-domain signal-averaging. Previous studies^{29,30} have demonstrated that this technique may be clinically useful, and preliminary data from our institution have shown that 8% of patients with chronic stable coronary artery disease have late potentials that cannot be detected by time-domain signal-averaging.¹⁹ In 11 cases (5%) of the present study, late potentials were detected only by time-domain signal-averaging due to an insufficient signal-to-noise ratio. However, in 5 cases (2.2%), late potentials were detected only by the high-resolution technique because of dynamic changes in morphology, duration, or timing of late potentials on a beat-to-beat basis, or a combination of these. Two of these 5 patients died suddenly during follow-up. This result deserves confirmation because it remains unknown whether ventricular late potentials with dynamic changes are more arrhythmogenic than those that are stable and constant.

Study limitations: This study was prospective, but patients were not randomized to treatment with or without thrombolytic agents. Possible systematic bias that would exclude the control group from thrombolysis are not completely excluded. However, because recent evidence demonstrates that thrombolysis improves survival,^{15,16} withholding such therapy for research purpose would be unethical. Moreover, both rt-PA and conventional treatment groups were matched with regard to most clinical variables (except age), and the incidence of late potentials in the control group was similar to the previously reported figures for patients after AMI.^{6,14} The technique for time-domain signal-averaging used in this study is different from the technique initially described by Simson.⁶ Abnormal criteria are derived from data obtained in normal subjects¹⁰ and are not strictly

comparable to criteria defined with other systems at different high-pass filter settings. The beat-to-beat technique is still experimental and needs further validation; however, this new technique may be helpful in identifying patients at risk of sudden death after AMI.^{19,29,30} Coronary angiography was performed in all patients <55 years old; for older patients, the decision to perform coronary angiography was based on the presence of residual chest pain or on a positive stress test, or both. Finally, the number of deaths and arrhythmic events in this study is too small to allow a definite conclusion about the prognostic significance of late potentials after AMI; however, our results confirm all previously published results.^{9,12,14}

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Late Outcome of Survivors of Out-of-Hospital Cardiac Arrest With Left Ventricular Ejection Fractions $\geq 50\%$ and Without Significant Coronary Arterial Narrowing

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In a retrospective survey of 1,195 survivors of out-of-hospital ventricular fibrillation, 43 patients were identified in whom left ventricular ejection fraction was ≥ 0.50 and in whom no coronary artery stenosis of $\geq 50\%$ luminal diameter were present. Thirteen (30%) of these patients had hypokinesia on left ventriculography, and 20 patients (47%) had a persistently abnormal electrocardiogram. Seven patients (16%) had recurrent out-of-hospital cardiac arrest during an average follow-up of 86 ± 54 months. The presence of either wall motion or electrocardiographic abnormalities defined patients with a several-fold higher risk of recurrent cardiac arrest than those without such abnormalities. The risk for recurrent cardiac arrest within 5 years was 30% in those with abnormal electrocardiograms versus 5% in the others ($p < 0.03$). Age was an independent predictor of recurrent cardiac arrest in this group ($p < 0.01$); surprisingly, recurrent cardiac arrest was occurring more often among younger patients.

Although cardiac arrest is unusual in patients without major structural heart disease, its recurrence in such survivors is common. Patients at relatively high risk for recurrent ventricular fibrillation can be identified by their youth and by abnormalities detected on the surface 12-lead electrocardiogram or by contrast left ventriculography.

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Victims of out-of-hospital cardiac arrest, even if young and ostensibly healthy, are usually found to have significant structural heart disease.¹⁻³ Previous studies in survivors have related the risk of recurrent cardiac arrest to the severity of coronary artery disease and to the severity of left ventricular (LV) dysfunction.^{4,5} Among survivors of ventricular fibrillation (VF) without such major structural heart disease, predictors of recurrent out-of-hospital cardiac arrest are less well defined. This study describes predictors of mortality and recurrent out-of-hospital cardiac arrest in patients whose cardiac evaluation after resuscitation identified no major structural abnormalities.

METHODS

Patients: The structure and components of Seattle's rapid response emergency care system have been reported previously.⁶ Since the inception of this program, a registry and follow-up of all patients resuscitated from out-of-hospital cardiac arrest have been maintained. Between March 1970 and March 1989, 5,105 patients were treated for out-of-hospital cardiac arrest, in whom VF was the first observed cardiac rhythm. Of 1,195 survivors of out-of-hospital VF, results of cardiac catheterizations were available in 528 patients. The patients had been initially treated in any of 14 Seattle hospitals, and the cardiac catheterizations were performed in 1 of 7 institutions. A retrospective survey of this population identified 43 survivors of out-of-hospital cardiac arrest who met all of the following criteria: (1) VF as the initial rhythm documented by the fire department paramedics, (2) performance of coronary angiography and contrast left ventriculography within 6 months of VF, (3) contrast LV ejection fraction ≥ 0.50 , and (4) no coronary artery stenoses of $\geq 50\%$ luminal diameter. Half of these 43 arrests occurred before 1981.

Evaluation: All data were analyzed without knowledge of patients' subsequent follow-up course. Historical, physical examination and laboratory records derived from hospital or clinic charts, paramedic incident reports and personal interviews were surveyed in all 43 patients.

Serial electrocardiograms from the 43 patients were available from at least the first 2 days after cardiac arrest, and were reinterpreted by ≥ 1 of us.

TABLE I Clinical Characteristics of Patients

Characteristics	No. of Patients (%)
Sex	
Men	33 (77)
Women	10 (23)
Prior medical history (not mutually exclusive)	
None	9 (21)
Hypertension	9 (21)
Chest pain	14 (33)
Myocardial infarction	1 (2)
Atrial arrhythmia*	9 (21)
Syncope/presyncope	3 (7)
Alcohol use	9 (21)
Heart murmur	3 (7)
Cigarette smoking	21 (43)
Activity at time of index cardiac arrest	
Sedentary	25 (58)
Physically active	13 (30)
Asleep	3 (7)
Unknown	2 (4)
Medications prescribed at time of index cardiac arrest	
None	27 (63)
Noncardiac	7 (16)
Diuretics	6 (14)
Digoxin	4 (9)
β blocker	4 (9)
Antiarrhythmic†	3 (7)
Admission serum potassium concentration (mEq/liter)	
≥ 3.2	33 (85)
2.7–3.1	6 (15)
Coronary arteries	
Normal	29 (67)
<50% diameter narrowing	14 (33)
10–20% narrowing	7 (16)
21–49% narrowing	7 (16)

* Paroxysmal atrial fibrillation, flutter or atrial tachycardia.

† For atrial arrhythmias.

Coronary angiograms and contrast left ventriculograms from all 43 patients were available and reviewed by 3 of the authors who were unaware of the identity of the patients. Coronary stenoses were measured on a projection screen with calipers and expressed as percent luminal diameter. Disagreements were resolved by consensus. LV wall motion and ejection fraction were assessed visually, and also quantitatively analyzed in the 30° right anterior oblique projection by the centerline and area-length methods, respectively.⁷ Wall motion abnormalities were localized to any of 5 LV wall segments (anterobasal, anterolateral, apical, inferior or posterobasal) during both visual and quantitative assessment. In 15 patients, quantitative left ventriculography could not be performed because of technical limitations, and LV function was assessed visually. The extent of additional testing and treatment in these 43 survivors of out-of-hospital cardiac arrest was individualized according to their physicians.

Follow-up: Follow-up was obtained annually for all patients by mailed questionnaires, by clinic visits, or by telephone contact with the patient, family or physician. In addition, paramedic records, hospital charts or medical examiners' reports were reviewed whenever patients

TABLE II Persistent Electrocardiographic Abnormalities

Electrocardiogram	n (%)
None (normal electrocardiogram)	23 (53)
T-wave inversion	4 (9)
Left ventricular hypertrophy with repolarization abnormality	3 (7)
>1-mm ST depression	3 (7)
Left bundle branch block	1 (2)
Left-axis deviation	2 (5)
>1-mm ST elevation	1 (2)
T-wave inversion & nonspecific ST changes	2 (5)
Atrial fibrillation, T-wave inversion & intraventricular conduction delay	1 (2)
Intraventricular conduction delay & T-wave inversion	1 (2)
Left-axis deviation & T-wave inversion	2 (5)

died or were rehospitalized. The duration of follow-up was calculated from the date of the initial cardiac arrest to: (1) recurrent cardiac arrest, (2) death from any cause, or (3) the most recent contact with the patient by mailed questionnaire (April 1989). Mean follow-up was 86 ± 54 months (range 7 to 201). Recurrent cardiac arrest was defined as an out-of-hospital unanticipated collapse attributed to a cardiac arrhythmia. This definition included fatal arrests, successful resuscitations, or discharge from an automatic implanted cardioverter-defibrillator that followed an abrupt loss of consciousness.

Data analysis: Statistical analyses were performed using Student's *t*, chi-square and Fisher's exact tests. A multivariate Mantel-Cox survival analysis model with stepwise variable selection was used to assess predictors of mortality and recurrent cardiac arrest. A Mann-Whitney analysis was used for nonparametric statistics. Values were considered insignificant at $p > 0.10$ (2-tailed).

RESULTS

Patients: Patients ranged in age from 20 to 73 years (mean \pm standard deviation 47 ± 13); 33 (77%) were men. Their other characteristics are listed in Table I. Although 34 patients (79%) had histories that might suggest cardiac abnormalities, none had recognized structural heart disease; none had a history of sustained ventricular tachyarrhythmias; and only 1 patient had a prior myocardial infarction (with an entirely normal coronary angiogram). At the time of cardiac arrest, most patients (63%) were not taking any medications, nor engaging in physical activity (70%). No patients sustained an arrest associated with acute ingestion of a toxic substance. Nearly half of the patients were habitual cigarette smokers.

Electrocardiograms: The patients had an average of 5 ± 2 electrocardiograms (range, 2 to 11; median, 5 tracings) performed over a mean of 8 ± 6 days (range, 2 to 25; median, 6) of hospital admission after cardiac arrest. Serial electrocardiograms remained abnormal in 20 of the 43 patients (47%) throughout their hospital

TABLE III Treatment of Patients During Follow-Up

Treatment	n (%)	Alive—No Recurrent Cardiac Arrest	Recurrent Cardiac Arrest	Other Death
No cardiac therapy*	12 (28)	9 (75%)	3 (25%)	0
Any cardiac therapy†	31 (72)	26 (84%)	4 (13%)	1 (3%)
β blocker	11 (26)	10 (91%)	1 (9%)	0
Calcium blocker	10 (23)	10	0	0
AICD	2 (5)	0	2	0
Digoxin	3 (7)	2 (67%)	0	1 (33%)
Antiarrhythmic	9 (21)	6 (67%)	2 (22%)	1 (11%)
Platelet inhibitor	7 (16)	7	0	0

* No significant differences in survival or recurrent cardiac arrest between treated and untreated patients.

† Listed therapies are not exclusive. For example, patients treated with both a β blocker and an antiarrhythmic drug are tabulated in both the β blocker and antiarrhythmic groups.

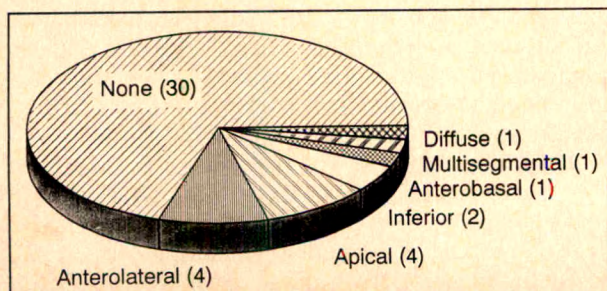
AICD = automatic implantable cardioverter defibrillator.

stay (Table II). However, none had persistent prolongation of the QT interval, preexcitation, or new or remote Q waves indicative of myocardial infarction. Electrocardiograms did not significantly change in any of the 23 patients (11 normal and 12 abnormal) who also had follow-up tracings available over a period of 292 ± 400 days (range 12 to 1,573) after hospital discharge.

Cardiac catheterization: Cardiac catheterization with coronary angiography and contrast left ventriculography was performed within 6 months of cardiac arrest in all patients, in 30 (70%) within 1 month after arrest. LV end-diastolic pressures were normal (≤ 12 mm Hg) in 27 of 38 patients (71%) in whom this measurement was available.

Thirteen patients (30%) had LV wall motion abnormalities (Figure 1). These were characterized (by visual assessment in all 43 patients, as well as by quantitative ventriculography in 28 patients) as focal hypokinesia in 11 patients (85%), multisegmental hypokinesia in 1 patient (8%), and diffuse hypokinesia in 1 patient. No patient had paradoxical LV wall motion or an aneurysm. Of the 4 cases (14%) in which there was disagreement between visual and quantitative assessment of LV wall motion, the quantitative analysis was reported (in all 4 cases, the visual interpretation was considered normal).

There was no consistent relation between the location of LV wall motion abnormalities and the anatomic distribution of any nonobstructive coronary artery stenoses ($<50\%$ diameter narrowing). Thus, among the 14 patients with nonobstructive coronary artery disease, 10

**FIGURE 1.** Prevalence and location of left ventricular wall motion abnormalities among 43 patients with out-of-hospital cardiac arrest.**TABLE IV** Predictors of Recurrent Cardiac Arrest (Multivariate Cox Analysis)

Group	No. of Pts.	Recurrent Cardiac Arrest (%)	p Value
Total group	43	7 (16)	
Left ventricular ejection fraction ≥0.6	28	3 (11)	<0.11
≥0.5 <0.6	15	4 (27)	
ECG			<0.03
Normal	23	1 (4)	
Abnormal	20	6 (30)	<0.06
Left ventricular wall motion			
Normal	30	3 (10)	<0.06
Abnormal	13	4 (31)	
ECG or wall motion			<0.08
Both normal	19	1 (5)	
Either abnormal	24	6 (25)	<0.01
Age*	43		

* Average age at the time of the index cardiac arrest was 37 ± 14 years for those who had recurrent arrest, compared with 49 ± 12 for those who survived without recurrent cardiac arrest ($p < 0.01$).

ECG = electrocardiogram.

patients (71%) had no LV wall motion abnormalities, 2 (14%) had wall motion abnormalities that corresponded to the distribution of the nonobstructive coronary artery lesions, and 2 others had wall motion abnormalities that did not correlate with the distribution of coronary stenoses.

As practices varied considerably in the 14 hospitals where patients were evaluated and treated, other diagnostic studies were not consistently performed. Similarly, treatment was selected and individualized by the patients' physicians. Overall, cardiac-directed therapy was not significantly associated with recurrent cardiac arrest or survival ($p > 0.3$) (Table III).

Predictors of recurrent cardiac arrest: The 43 patients experienced a total of 7 recurrent cardiac arrests (16%): 3 fatal and 2 successful resuscitations, as well as 2 others who received a discharge from an implanted automatic cardioverter-defibrillator. By Cox multivariate survival analysis, the presence of either persistent electrocardiographic or segmental LV wall motion abnormalities during contrast ventriculography defined patient groups with a higher risk of recurrent cardiac arrest during follow-up (Table IV). For example, the risk for recurrent cardiac arrest within 5 years was 30% in those with abnormal electrocardiograms compared with 5% in the others ($p < 0.03$, Figure 2A). Among patients with preserved global ejection fraction, but with a wall motion abnormality, the risk for recurrent arrest within 5 years was 35%, compared with 10% in the others ($p < 0.06$, Figure 2B). In patients with either an abnormal electrocardiogram or wall motion abnormality, the risk for recurrent cardiac arrest within 5 years was 26%, compared with 6% in those with a normal electrocardiogram and no wall motion abnormality ($p < 0.08$, Figure 2C). Neither the location of the LV wall motion

abnormality nor the nature of the electrocardiographic irregularity were individually predictive of recurrent cardiac arrest.

Age was also found to be a predictor of recurrent cardiac arrest in this group. Surprisingly, age was a negative independent predictor: younger patients fared less well than older. Patients in whom cardiac arrest recurred were younger at the time of their initial event (37 ± 14 years) than those without recurrent cardiac arrest (49 ± 12 years, $p < 0.01$).

DISCUSSION

Cardiac arrest in patients without major structural heart disease is unusual.^{6,8} The cause of VF in such patients is typically obscure; drug abuse, primary conduction system disease, coronary artery spasm and subclinical myocarditis have all been reported as potential etiologies.⁹⁻¹³ Many diagnostic and therapeutic interventions in this frequently young and ostensibly healthy group of patients are possible. The extent of evaluation or optimal treatment largely hinges on the identification of those at high risk for recurrent sudden cardiac death.

Previous studies of out-of-hospital VF have focused predominantly on patients with significant atherosclerotic coronary artery disease. In such persons, the risk of recurrent cardiac arrest is approximately 20% during the first year, and as high as 58% at 5 years.¹⁴ Recurrence in these patients has been linked to the presence of widespread obstructive coronary artery disease, lower ejection fraction and more severe abnormalities of LV contraction.^{4,15} The prognosis in survivors of cardiac arrest without obstructive coronary artery disease and with preserved LV ejection fraction has not been defined. However, the present study demonstrates that recurrent cardiac arrest in such patients is common and is far in excess of observed mortality in a comparably aged population without coronary artery disease (<1% per year).¹⁶

The salient findings of this study suggest that resuscitated patients without major structural heart disease can be stratified for risk of recurrent sudden death syndrome by age and by abnormalities on the 12-lead electrocardiogram or on left ventriculography. Younger patients, and those with persistent electrocardiographic or LV wall motion abnormalities after cardiac arrest, comprise a group with a several-fold higher risk for recurrent cardiac arrest.

By what mechanism might such abnormalities predispose to recurrent VF? It has been suggested that patterns of regional LV wall motion may be associated with intramyocardial conduction asynchrony, which, in turn, may be a precondition for initiating and sustaining VF.¹⁷ Disruption of the normal surface electrocardiographic pattern could also serve as another expression of such intramyocardial conduction asynchrony, and predisposition to VF. Why younger patients fare more poorly than older patients is less clear. Perhaps cardiac arrest in a younger individual identifies a more seriously deranged or unstable substrate than that in older victims.

Study limitations: This is a descriptive, retrospective study of resuscitated patients, selected by normal or

near-normal cardiac catheterization findings. Acute thrombosis (with spontaneous thrombolysis) or spasm at the site of an insignificant coronary artery lesion could have precipitated cardiac arrest in some patients. However, no relation was observed between the location

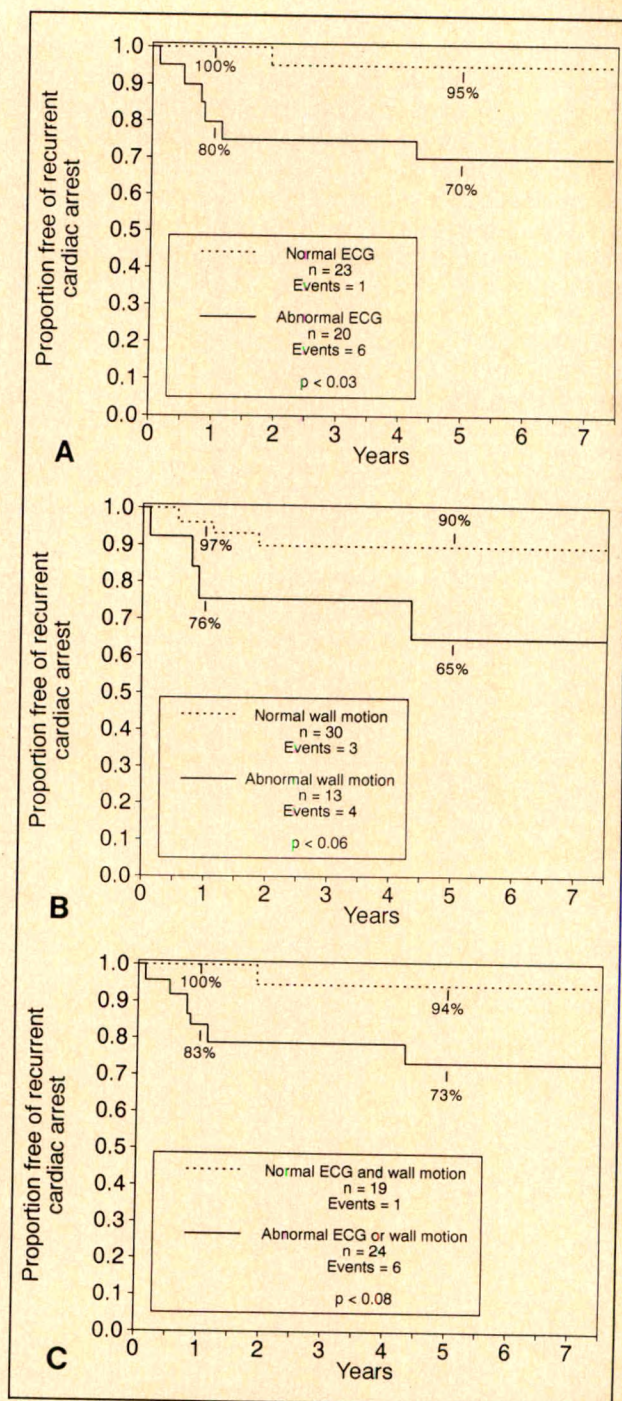


FIGURE 2. Cumulative survival free of recurrent cardiac arrest in 43 patients with out-of-hospital cardiac arrest (Mantel-Cox multivariate analysis). Survival is shown for patients: **A**, with a normal electrocardiogram (ECG) versus patients with an abnormal electrocardiogram; **B**, with normal left ventricular wall motion versus patients with abnormal left ventricular wall motion; **C**, with a normal electrocardiogram and normal left ventricular wall motion versus patients with either an abnormal electrocardiogram or left ventricular hypokinesia. In each plot, the percent survival is shown at 1 and 5 years.

of LV wall motion abnormalities and the anatomic distribution of any nonobstructive coronary artery narrowings to raise suspicion for such a cause. Other diagnostic studies, such as exercise testing, endomyocardial biopsy, invasive electrophysiologic testing or ergonovine challenge were not consistently performed, and therefore the predictors of recurrent cardiac arrest defined by this study are not necessarily exhaustive. Therapy was not prospectively assigned, but the effect of no cardiac therapy versus any cardiac therapy on survival after cardiac arrest did not appear to be significant. However, given the higher frequency of recurrent cardiac arrest in younger patients and in those with electrocardiographic or LV wall motion abnormalities, such survivors merit close scrutiny and consideration for aggressive intervention.

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Comparison of Clinical and Electrophysiologic Features of Preexcitation Syndromes in Patients Presenting Initially After Age 50 Years with Those Presenting at Younger Ages

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Although patients may develop arrhythmias due to preexcitation syndromes at any time from the prenatal period to late adulthood, presentation in late adulthood is considered uncommon and has not been well studied. From June 1981 to June 1989, 73 patients were documented to have preexcitation syndromes on the basis of electrophysiologic studies. Those whose initial arrhythmias appeared at an age >50 years (group 1, $n = 13$) were compared with the remaining 60 patients (group 2).

All group 1 patients presented in the setting of acute medical or surgical diseases ($n = 7$), or chronic cardiac disease ($n = 6$) commonly associated with middle age and often with atrial arrhythmias; only 13 group 2 patients had underlying illnesses ($p = 0.0001$). Almost two-thirds of group 2 patients were evaluated because of narrow complex orthodromic tachycardia or palpitations and electrocardiographic evidence of preexcitation. Wide complex tachycardia was more often a reason for referral of older patients (7 of 13 vs 11 of 60, $p < 0.05$), among whom atrial fibrillation/flutter also tended to be more frequent (4 of 13 vs 11 of 60, difference not significant). The PR and QRS intervals of group 1 patients were within the normal range and differed significantly from those of group 2 patients (PR, 0.15 ± 0.04 vs 0.11 ± 0.03 second, $p < 0.001$; QRS, 0.09 ± 0.01 vs 0.12 ± 0.03 second, $p < 0.001$), making electrocardiographic identification of preexcitation more difficult in group 1. Several factors likely contributed. Concealed bypass tracts tended to appear more frequently in older patients (5 of 13 vs 8 of 60, $p = 0.047$), but intraatrial conduction delays as measured by the P-wave duration (103 ± 21 vs 90 ± 16 ms, $p = 0.023$), and the time from the onset of the P wave to the low right atrial electrogram (48 ± 19 vs 38 ± 15 ms, $p = 0.042$) may have contributed.

Thus, as in infancy, specific age-related descriptors characterize patients presenting with preexcitation syndromes over the age of 50 years. Awareness of these descriptors will facilitate care of these adults.

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Since the initial report of "Bundle branch block with short P-R interval in healthy young people prone to paroxysmal tachycardia,"¹ preexcitation syndromes have been most extensively described in infants and children.²⁻⁹ Although patients may develop symptoms due to these syndromes at any age, presentation in late adulthood has been thought to be uncommon and has not been well studied. Several distinctive age-related presentations of preexcitation syndromes have been described, including hydrops and congestive heart failure in association with narrow complex tachycardia in the prenatal period and during infancy,⁹ and exercise-related palpitations or orthodromic tachycardia in adolescence and early adulthood.⁴ It is the purpose of this study to identify and characterize a group of patients whose initial symptoms due to a preexcitation syndrome appeared after the age of 50 years.

METHODS

Patients: From June 1981 to June 1989, 73 patients were documented to have preexcitation syndromes at electrophysiologic studies performed in the Adult Cardiac Electrophysiology Laboratory of the Yale-New Haven Hospital. Patient records were reviewed and 13 patients >50 years old at the time of their initial symptoms were identified. They form the study population (group 1). They were compared with the remaining 60 patients who were ≤ 50 years old at the time of their presenting symptoms (group 2).

Initial symptoms began appearing in group 1 patients at a mean (\pm standard deviation) age of 63 ± 8 years; patients underwent electrophysiologic testing at age 66 ± 6 years. Symptoms began appearing at age 18 ± 13 years in group 2 patients, who were aged 31 ± 15 years at the time of study. The youngest group 2 patient was 6 years old, and although 9 group 2 patients were >50 years old at the time of evaluation, they had had symptoms for many years. The time from the onset of

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symptoms to study was shorter in group 1 (3 ± 3 vs 13 ± 13 years, $p < 0.001$). The groups did not differ in sex distribution (6 of 13 vs 34 of 60 men, difference not significant).

Electrophysiologic studies: Electrophysiologic evaluations were performed with standard techniques,¹⁰ in the postabsorptive drug-free state after informed consent was obtained. "Wide complex tachycardia" was defined as a regular tachycardia with a wide (>0.12 second) and sometimes bizarre QRS complex, for which the exact diagnosis was often not certain at the time of initial referral to the electrophysiology service.

Statistics: Categorical data were evaluated by chi-square analysis with Yates' correction or Fisher's exact test. Numerical data were analyzed by the Student *t* test for unpaired data and, where appropriate, the Wilcoxon rank sum test. The CLINFO computer resource was used for data analysis. Data are expressed as mean \pm standard deviation. Statistical significance is defined as $p < 0.05$.

RESULTS

A number of clinical and electrophysiologic characteristics of group 1 patients, who represent 18% of those studied in our laboratory during this period and found to have preexcitation syndromes, differ significantly from those of the younger patients.

All 13 older patients presented with their initial arrhythmia in the setting of acute medical or surgical diseases, or chronic structural or electrical heart disease often associated with middle age. Significantly fewer (13 of 60) group 2 patients had associated cardiac or systemic illnesses at the time of presentation ($p = 0.0001$). Among the younger patients, 4 had cardiomyopathies (hypertrophic in 1), 4 had asthma (mild and not associated with acute arrhythmias in 3), 3 had valvular/congenital heart disease (1 with Ebstein's anomaly), and 2 had hypertension/angina. Group 1 patients

with chronic heart disease included 3 with atrial disease (including the tachy-brady syndrome in 2), 2 with coronary artery disease and 1 with aortic regurgitation and a reduced ejection fraction. Initial arrhythmias appeared in the early postoperative period in 3 older patients: 1 after cholecystectomy, 1 after hip replacement, and 1 after coronary artery bypass grafting; the latter patient had rapid atrial fibrillation after surgery that responded paradoxically to digoxin. Three group 1 patients had pulmonary disease: 1 had severe chronic obstructive lung disease, 1 had asthma, and 1 had an acute pulmonary embolus. The remaining patient had had a gastrointestinal hemorrhage and was anemic.

Almost two-thirds of the group 2 patients were evaluated because of narrow complex orthodromic supraventricular tachycardia, or palpitations in the setting of overt preexcitation revealed on an electrocardiogram (Figure 1). No group 1 patient was studied for this latter indication. The groups were distinguished by the clinical arrhythmias documented before study (Figure 2). Only 15% (2 of 13) of group 1 patients presented with narrow QRS orthodromic supraventricular tachycardia. Wide QRS tachycardia was significantly more frequent (7 of 13 vs 6 of 60, $p < 0.05$) in this group and on several occasions was initially mistaken for ventricular tachycardia. Among the older patients, wide complex tachycardia was due to aberration in 4 patients with orthodromic tachycardia, antidromic supraventricular tachycardia in 2, and atrial flutter with 2:1 conduction over the accessory pathway in 1. The distribution was similar in the 6 younger patients with this arrhythmia: 3 with aberration, 2 with antidromic supraventricular tachycardia, and 1 with preexcited atrial flutter.

Atrial fibrillation/flutter also tended to be more frequent among group 1 patients, although this difference did not reach statistical significance (4 of 13 vs 11 of 60, difference not significant). None of the 4 group 1 patients with this clinical arrhythmia had a sustained reentrant supraventricular tachycardia induced in the electrophysiology laboratory. This had several causes,

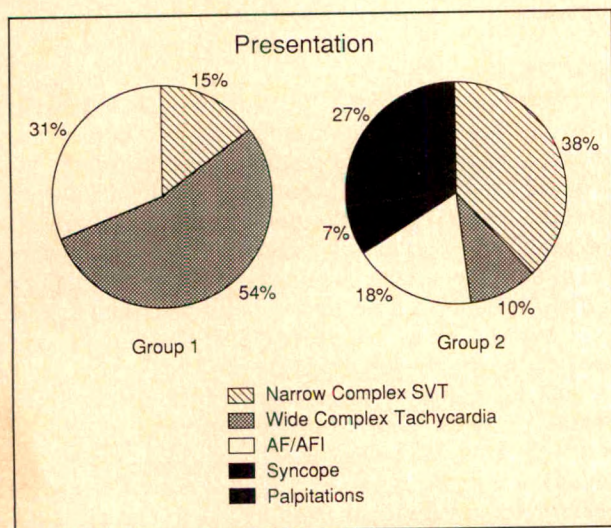


FIGURE 1. Comparison between the reasons for referral of group 1 and group 2 patients. AF/AFI = atrial fibrillation/flutter; SVT = supraventricular tachycardia.

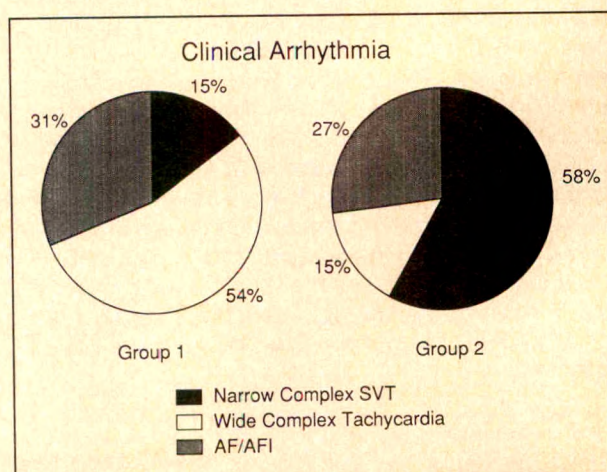


FIGURE 2. Comparison of the documented clinical arrhythmias of group 1 and group 2 patients. Abbreviations as in Figure 1.

including distal block in the normal conduction system, a prolonged accessory pathway refractory period, and matched refractory periods of the accessory pathway and normal conduction system. All had inducible atrial fibrillation. In contrast, all 11 group 2 patients with atrial fibrillation/flutter clinically had supraventricular tachycardia induced ($p = 0.013$).

As Figure 3 shows, surface electrocardiographic findings often made it difficult to identify group 1 patients as having preexcitation syndromes. Although individual older patients were preexcited at rest, the PR and QRS intervals for this group as a whole were within the normal range, and differed significantly from the values for the younger patients (Table I). Concealed bypass tracts were more frequent in group 1 (5 of 13 vs 8 of 60 patients), but this difference is of borderline significance ($p = 0.047$) and, when only patients with anterograde conduction over their accessory pathways are considered, the electrocardiographic differences persist (Table I). These differences also cannot be accounted for by differences in the location of the accessory pathways or their mean anterograde refractory periods. Left-sided pathways were most frequent in both groups (Figure 4), and the refractory periods of these connections in the 8 group 1 patients with anterograde conduction (328 ± 118 ms) did not differ significantly from those of 46 of the 52 group 2 patients for whom data are available (354 ± 157 ms, difference not significant). Four group 1 and 25 group 2 patients (difference not significant) had pathways with anterograde refractory periods of ≤ 300 ms.

Intraatrial conduction times as measured by P-wave duration on the surface electrocardiogram (103 ± 21 vs

TABLE I Surface Electrocardiogram Characteristics

	Group 1	Group 2	p Value
All Patients			
n	13	60	
PR (s)	0.15 ± 0.04	0.11 ± 0.03	<0.001
QRS (s)	0.09 ± 0.01	0.12 ± 0.03	<0.001
Patients with Anterograde Conduction			
n	8	52	
PR (s)	0.15 ± 0.03	0.10 ± 0.03	<0.001
QRS (s)	0.09 ± 0.02	0.12 ± 0.03	<0.001

90 ± 16 ms, $p = 0.023$) and the interval from the onset of the P wave to the low right atrial electrogram (48 ± 19 vs 38 ± 15 ms, $p = 0.042$) were longer, however, in group 1 patients.

DISCUSSION

Previous studies examining age-specific presentations of the preexcitation syndromes have focused on infancy and childhood²⁻⁹; few have examined these syndromes in older patients.¹¹⁻¹⁴ Our study demonstrates that age-related disease states, changes in the accessory pathway and the heart itself distinctively affect the presentation of these syndromes in older patients.

In 2 studies of patients with electrocardiographic evidence of the Wolff-Parkinson-White syndrome, approximately 20% were ≥ 50 years of age^{11,13} when identified. However, in the latter study,¹³ only 6% had their initial arrhythmia when ≥ 50 years old. Eighteen percent of our patients with accessory pathways had their initial clinical event when they were >50 years old, emphasizing the importance of recognizing the unique clinical characteristics of these syndromes in older patients.

Because we examined our patients at only one point in time, it is not possible to define exactly the electrophysiologic changes that facilitated the new onset of arrhythmias not seen earlier in life. However, several factors seem likely. Although the Wolff-Parkinson-White syndrome has been associated with a 20 to 46% incidence of structural heart disease^{2,3,8,9} (characteristical-

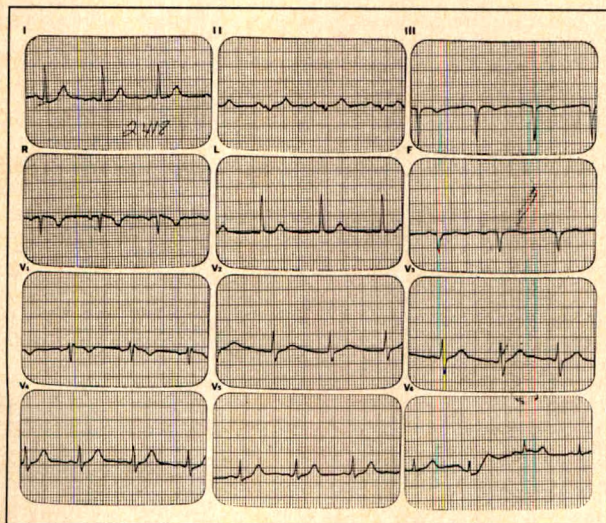


FIGURE 3. Standard surface electrocardiogram of a group 1 patient. Note the PR interval of 0.16 second and the QRS interval of 0.09 second, as well as the pseudoinferior wall myocardial infarction pattern. This patient presented with a wide complex tachycardia due to atrial flutter, with 2:1 conduction over a left posterior accessory pathway after a hip replacement. He was initially, incorrectly, thought to have ventricular tachycardia in the setting of an old inferior wall myocardial infarction.

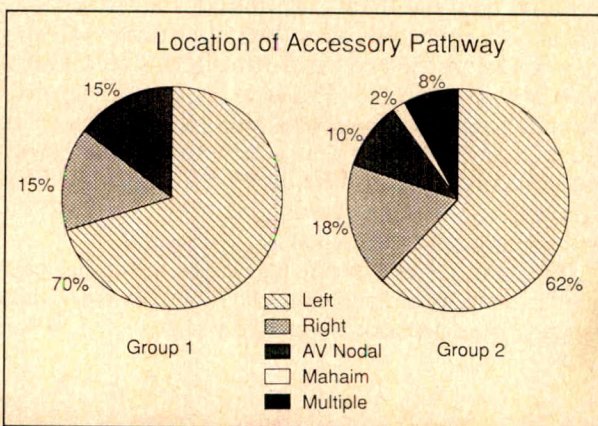


FIGURE 4. Anatomic distribution of accessory pathways in groups 1 and 2. AV = atrioventricular (intranodal).

ly congenital heart disease and specifically Ebstein's anomaly) in infants and children, the majority of young patients are healthy, with otherwise normal hearts when they first have arrhythmias. In contrast, all our older patients presented in the setting of a medical or surgical illness, and 7 were acutely ill. Several of these illnesses have well-known associations with atrial arrhythmias, and an increase in inciting events (atrial premature contractions) certainly contributed to the incidence of atrial fibrillation and may have led to the new onset of supraventricular tachycardia in some patients.

All 4 of our patients who presented with atrial fibrillation did not have a sustained reciprocating tachycardia induced during their electrophysiologic studies. They are similar to the asymptomatic patients with electrocardiographic evidence of preexcitation described by Milstein et al,¹⁵ in that they have a "deficient substrate" for the maintenance of reentrant tachycardia. Only with other precipitants (illness) did they have atrial fibrillation. As these authors suggest, and our study emphasizes, despite the absence of supraventricular tachycardia, such patients will remain vulnerable to complications because of the presence of an accessory pathway in the setting of other degenerative or inflammatory processes. Furthermore, different mechanisms are thus suggested for the initiation of atrial fibrillation in our 2 patient groups: atrial vulnerability in group 1 and degeneration of supraventricular tachycardia in group 2.

The arrhythmia most frequently observed in patients with accessory pathways is a narrow complex orthodromic tachycardia. Our group 1 patients differed from the younger patients, and those of other series,³ in that 54% presented with a wide complex, regular tachycardia. In this late adult age range, in the setting of an underlying illness and an electrocardiogram that often demonstrated a pseudoinfarction pattern without marked preexcitation (Figure 3), misdiagnoses of ventricular tachycardia were made several times. Although such patients comprise the minority of those with a wide complex tachycardia, sensitivity to the possibility of preexcitation is essential if such syndromes are to be suspected and correctly diagnosed.

It has been shown that the capacity for preexcitation and anterograde conduction over an accessory pathway may be lost over several years and that this occurs more often in older patients.¹⁴ This is consistent with our finding that concealed pathways were more frequent in group 1. However, this is not the only explanation for the relatively unimpressive electrocardiographic findings of group 1, which persist even when only patients with anterograde conduction are considered.

Both the P-wave duration and the intraatrial conduction time were significantly longer in group 1 than group 2. Age and disease probably contributed to this

difference, as 3 of our older patients had definite electrical abnormalities of the atrium. Atrial conduction delays would mask anterograde conduction over a left-sided accessory pathway, which is far from the normal origin of the sinus impulse, but perhaps also over other pathways located at a distance from the specialized intraatrial conduction system, minimizing evidence of preexcitation, and normalizing electrocardiographic intervals.

Clinical implications: Our findings emphasize that patients may initially present with arrhythmias due to preexcitation syndromes throughout life, including late adulthood, when the clinical features of these syndromes are different from those in younger patients. Diagnosis may be challenging. An awareness that such patients present in the setting of acute or chronic illness, most often with a wide complex tachycardia or atrial fibrillation/flutter, and often with subtle or no baseline electrocardiographic evidence of preexcitation, will facilitate their care.

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Usefulness of Flecainide for Prevention of Paroxysmal Atrial Fibrillation and Flutter

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To evaluate the efficacy of flecainide acetate in the prevention of paroxysmal atrial fibrillation and flutter, 43 patients (23 men) (mean age 53 years) were randomized blindly to receive either placebo or 150 mg of flecainide twice per day for consecutive periods of 3 months. Attacks were verified by a minielectrocardiogram event recorder. If intolerable symptoms developed, the protocol allowed patients to cross over between treatments before the end of the first 3-month period. Four patients crossed over prematurely, between 1 week and 1 month, and 15 between 1 month and 3 months. The remaining 24 patients completed both 3-month periods. In all 3 treatment intervals, there was a significant reduction in the number of attacks during flecainide treatment ($p < 0.002$). Complete suppression was seen in 15 of 43 patients (35%) treated with flecainide for 1 week, in 18 of 39 (46%) treated for 1 month and in 12 of 24 (50%) completing all 3 months in each period. Adverse effects were reported in 32 of the 43 patients (74%) treated with flecainide, but only 2 were withdrawals. One patient died suddenly. In comparison, 3 of 43 patients (7%) reported adverse effects in the placebo group. In conclusion, flecainide significantly suppressed the number of attacks of paroxysmal atrial fibrillation and flutter. Adverse effects were frequent but were mostly tolerable.

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Flecainide acetate is a class IC antiarrhythmic drug with potent sodium channel-blocking properties and with little effect on the duration of the action potential. Several studies have shown an effect on ventricular arrhythmias¹⁻³ but less is known about the effect on supraventricular arrhythmias. Atrial fibrillation is a common and clinically important arrhythmia with a prevalence of about 0.4% in the population <70 years, and of 2 to 4% above this age.^{4,5} Such patients are at an increased risk of embolic complications.⁶ There have been no previous double-blind crossover studies documenting the effect of flecainide in the prevention of paroxysmal atrial fibrillation and flutter. The purpose of the present study was to evaluate the ability of flecainide to prevent attacks of atrial fibrillation and flutter in a double-blind, controlled, crossover study.

METHODS

Patients: The main criterion for inclusion in the study was ≥ 3 clearly symptomatic attacks of atrial fibrillation or flutter, or both, in the preceding 3 months, on 3 different days, each attack lasting ≤ 3 days (qualifying period). At least 1 attack had to be documented by electrocardiography.

Pregnant or breast-feeding women were excluded, as well as patients with progressive valvular disease, heart failure in New York Heart Association class III to IV or with an abnormal fractional shortening on echocardiography, grade ≥ 2 atrioventricular block, more than isolated ventricular premature complexes, sinus node dysfunction without a pacemaker, Wolff-Parkinson-White syndrome, syncope, thyroid disease, or other significant systemic disease.

Protocol: The protocol was approved by local ethics committees. Patients gave informed consent based on written and oral information. The patients were investigated with a 12-lead electrocardiogram, chest x-ray, echocardiography and standard blood chemistry analyses, including kidney and liver function tests. Patients were seen 3 times in each period (after 1 week, 1 and 3 months), with plasma-flecainide concentrations measured after 1 week and 3 months. The plasma level (checked by a colleague) was not to exceed $2.11 \mu\text{mol/liter}$ ($1,000 \mu\text{g/liter}$).

Treatment: Patients were randomized double-blindly to receive either 150 mg of flecainide twice per day (patients < 60 kg, 100 mg twice per day) or matching placebo for a 3-month period, after which they were crossed over to the alternate therapy for a further 3-month period. If intolerable symptoms developed, the

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*See Appendix.

TABLE I Mean Attacks per Week for Patients Who Crossed Over (n = 4) or Terminated Treatment Prematurely (n = 15) Compared with Patients Who Completed Both Periods (n = 24)

	1 Week	1 Month	3 Months
Placebo (n = 4)	12.3 ± 6.4 (n = 4)	2 (n = 1)	0 (n = 0)
Flecainide (n = 4)	8.0 ± 6.8 (n = 4)	3.0 ± 3.0 (n = 3)	5.2 (n = 1)
Placebo (n = 15)	3.0 ± 3.4 (n = 15)	3.3 ± 3.3 (n = 15)	0 (n = 2)
Flecainide (n = 15)	3.1 ± 9.4 (n = 15)	1.2 ± 1.7 (n = 15)	0.6 ± 1.4 (n = 11)
Placebo (n = 24)	4.1 ± 7.3 (n = 24)	2.4 ± 5.5 (n = 24)	1.9 ± 12.1 (n = 24)
Flecainide (n = 24)	0.9 ± 1.5 (n = 24)	0.4 ± 0.9 (n = 24)	0.2 ± 0.4 (n = 24)

protocol allowed discontinuation of the first treatment and cross over to the second before the end of the first 3-month period. Digitalis glycosides were allowed at the discretion of the investigator and were recommended for patients with known atrial flutter. No other antiarrhythmic therapy was allowed. The patients were explicitly asked to list side effects at each visit.

Evaluation: Patients kept a diary to record symptoms and duration of attacks. At least 2 of these attacks (if any) in each period had to be verified by an electrocardiogram. For that purpose the patients kept a handheld minielectrocardiogram event recorder constructed

on the basis of an ordinary Walkman™, with some of the electronics replaced by an amplifier, a high-pass filter and a frequency modulator. The electrocardiogram was recorded with the patient in a relaxed, sitting position, with the fingers from both hands held against the electrodes. Data were stored on an ordinary cassette tape with a recording capacity of ≥1 hour. The signals were reproduced by a tape deck, with a demodulator connected to an ordinary electrocardiogram recorder. The electrocardiogram was interpretable in almost all recordings.

Patients were not included in the study if a lack of correlation was found between the diary and the minitape recordings from lack of compliance or inability to complete the study for reasons unrelated to the study medication.

Statistics: Medians with 1.0 and 3.0 quartiles and means ± 1 standard deviation are given. The attack rates within each period were compared with Wilcoxon's test, based on ranks.

RESULTS

Patients: Forty-eight patients were recruited for the study. Five dropped out: 2 developed chronic atrial fibrillation in the first period while receiving placebo, 1 patient died in the first period while receiving flecainide, and 2 could not follow the protocol. The evaluated group comprised the remaining 43 patients (Figure 1), 23 men and 20 women, aged 21 to 73 years (mean 53 ± 13). The average weight was 77 ± 14 kg (range 55 to 104). Three patients had ischemic heart disease, 2 had hypertension, and 1 slight mitral valve disease. One patient was in New York Heart Association functional class 2; all others were in class 1. All patients had paroxysmal atrial fibrillation, but 7 also had attacks of atrial flutter. The history of attacks was in median 7 years (range 0 to 33). The median number of previous antiarrhythmic drugs was 2 (range 0 to 7). Concomitant digitalis glycosides were given to 13 patients.

Treatment: All 43 patients were treated for ≥1 week in each period but, because of intolerable attacks of arrhythmia or adverse effects, 4 had to cross over after the first week in the first period (1-week interval), 3 patients while receiving placebo and 1 while receiving flecainide (Figure 1, Table I). The remaining 39 patients were treated for ≥1 month with both regimens (1-month interval), when an additional 15 had to cross over or terminate the drug prematurely because of intolerable attacks of arrhythmia. Among these patients, 11 were receiving placebo and 4 flecainide. The last 24 patients completed all 3 months in both periods. For statistical reasons, each treatment interval was evaluated separately (Table II). In all 3 treatment intervals, there was a significant reduction in the number of attacks (2p ≤ 0.003) in the flecainide-recorded period. The individual responses are shown in Figure 2. Complete suppression with flecainide was seen in 35% of the patients treated for 1 week with both regimens, in 46% treated for 1 month and in 50% completing all 3 months (Table III).

PLASMA-FLECAINIDE: The plasma level after 1 week of treatment was 1.24 ± 0.49 μmol/liter (range 0.51 to

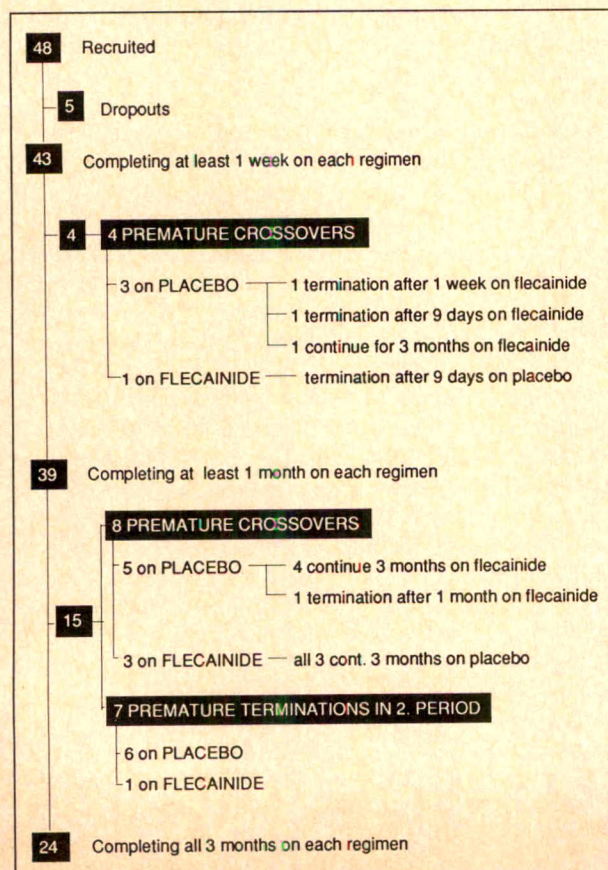


FIGURE 1. Flow chart for all study patients.

TABLE II Results After Treatment with Flecainide

Treatment	P	F	P	F	P	F
Sample size	43	43	39	39	24	24
No. of attacks						
Median	2	0	6	0	10	0
Range	0-30	0-37	0-124	0-60	0-324	0-35
1.0-3.0 quartile	1-4	0-2	3-12	0-4	4-23	0-7
Difference (Wilcoxon/ranks)	2p = 0.003		2p = 0.0002		2p = 0.001	
F = flecainide; P = placebo.						

2.30) and, at the end of the treatment period, was $1.03 \pm 0.47 \mu\text{mol/liter}$ (range 0.24 to 2.42). The plasma concentrations tended to be a little higher in the group with efficacy with flecainide treatment: 1.08 (range 0.24 to 1.82) versus 0.87 (range 0.63 to 0.97) $\mu\text{mol/liter}$ (3-month treatment period).

Adverse effects: Thirty-two of the 43 patients (74%) reported a total of 51 complaints of adverse effects in the flecainide treatment period (Table IV). The cardiovascular complaints included exercise dyspnea and edema in 1 patient and bradycardia in 1. Two patients had an increase in attack rate, which resulted in the discontinuation of treatment in 1 patient. Another developed a sustained attack of atrial flutter with intermittent 1:1 conduction, which also resulted in discontinuation (plasma-flecainide 1.21 $\mu\text{mol/liter}$). Two patients had their dosage reduced because of dizziness (plasma-flecainide level not available) and problems with accommodation (plasma-flecainide 1.06 $\mu\text{mol/liter}$), respectively, with disappearance of their symptoms. In the placebo period, 3 of the 43 patients (7%) experienced a total of 6 adverse effects: leg cramps in 2 patients, sweating in 2, headache in 1 and transient limpness of the left arm in 1.

Two patients died during the investigation period. One patient receiving flecainide died from an anaplastic pulmonary carcinoma with metastases to the brain. Retrospectively, a pulmonary infiltration could be discerned on the chest x-ray taken before the patient was included in the study. The other patient died suddenly after 2 months' treatment with flecainide, while bathing in the cold, northern Norway sea after drinking alcohol. Plasma-flecainide level in this patient was 0.5 $\mu\text{mol/liter}$ at the 1-week visit. The incident was not interpreted

as a complication of flecainide treatment. One patient had a myocardial infarction.

Electrocardiographic measurements revealed a slight increase in all intervals: PQ from 0.17 to 0.19, QRS from 0.09 to 0.10, and QTc from 0.40 to 0.41 second. There were no changes in blood biochemistry values.

DISCUSSION

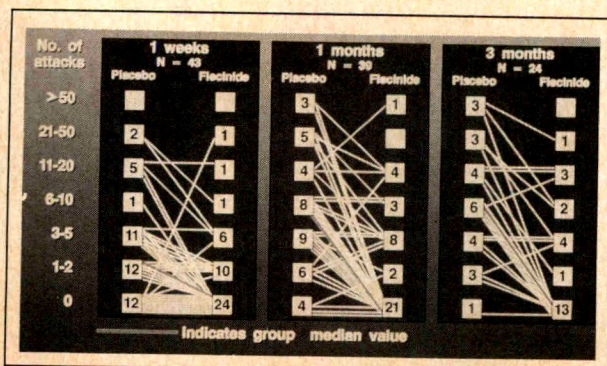
Evaluation of patients with paroxysmal tachycardias: One of the problems in evaluating antiarrhythmic drug efficacy is the marked spontaneous variability of arrhythmias. Holter monitoring is widely used but has severe limitations in patients with days or weeks be-

TABLE III Response to Flecainide Treatment

Duration (wks)	Complete (%)	Partial (%)	No/Worse (%)
1	15 (35)	8 (19)	19/1 (47)
4	18 (46)	8 (21)	10/3 (33)
12	12 (50)	4 (17)	8/0 (33)

TABLE IV Adverse Effects with Flecainide (n = 32 of 43 [74%])

Adverse Effects	No.	Total No.
Dizziness		11
Gastrointestinal		12
Constipation	6	
Diarrhea	1	
Nausea	3	
Feeling of satiety	1	
Meteorism	1	
Eye disturbances		11
Blurred vision	7	
Accommodation	2	
Dry eyes	1	
Slight nystagmus	1	
Cardiovascular		6
Proarrhythmia	3	
Weight gain	1	
Exercise dyspnea	1	
Bradycardia	1	
Tiredness		3
Amenorrhea		1
Dry mouth		1
Tingling in scalp		1
Urge incontinence		1
Paresthesia in legs		1
Tinnitus		1
Flushing		1
Headache		1
Total		51

**FIGURE 2.** Individual response for all 3 treatment intervals after flecainide treatment.

tween attacks, as found with paroxysmal atrial fibrillation and flutter. One way to register the frequency of attacks of tachyarrhythmias during longer periods is to use diaries. An easy way to verify attacks has been lacking. For that purpose, we used small custom-made, hand-held event-recorders. In the present study, ≥ 2 attacks were verified objectively by the event-recorder in each period, except for patients free of attacks. Patients were not included if there was a lack of correlation between attacks noted in their diaries and the event recordings. A good correlation was found in all cases included in the study. We found the event-recorder especially useful in the qualifying period, because some of the patients not included were in sinus rhythm during their "attacks."

Flecainide efficacy: We found flecainide to be very effective against paroxysmal atrial fibrillation and flutter, with a highly significant reduction in the numbers of attacks in all 3 treatment intervals ($2p \leq 0.003$). Complete suppression with flecainide was achieved in 35% of the patients treated with both regimens for only 1 week, in 46% treated for 1 month and in 50% treated for 3 months (Table III). The lowest efficacy was found in patients treated for only 1 week and 1 month; this is not surprising, because these periods comprise the patients with the most severe and frequent attacks, when 4 and 15 patients, respectively, had to cross over or discontinue the treatment prematurely (Table I). These results are in accordance with preliminary reports of 2 other double-blind, crossover studies showing response rates of 56 and 28%, respectively.^{7,8} In 2 non-placebo controlled studies, the success rates were 60 and 87%.^{9,10} In a study evaluating drug-refractory (including amiodarone) paroxysmal atrial fibrillation, flecainide alone controlled the arrhythmia in 28% and the combination of flecainide and amiodarone in 53%.¹¹

Long-term efficacy in paroxysmal atrial fibrillation was evaluated in an open study with a total response in 60%.¹² Another open study compared flecainide with disopyramide in maintaining sinus rhythm after conversion of chronic atrial fibrillation. Flecainide had a substantially greater effect than disopyramide.¹³

Adverse effects: We found a relatively high rate of adverse effects (74%), which resulted in discontinuation of flecainide treatment in 2 patients because of proarrhythmic effects. One of these developed a sustained attack of atrial flutter with intermittent 1:1 conduction, even though he was treated with digoxin. This is a potentially dangerous complication, also known to occur with other class I antiarrhythmic drugs. Known atrial flutter is the reason why concomitant digoxin is recommended. Despite this, the patient developed 1:1 conduction with a relatively low serum digoxin concentration of 0.8 nmol/liter.

One patient, a 54-year-old man, receiving treatment with flecainide died suddenly. He had been operated on in 1962 for hyperthyroidism, with recurrence in 1976 and carbimazol treatment until 1985. Since 1986 he had had paroxysmal atrial fibrillation, treated unsuccessfully with propranolol, digoxin, quinidine, disopyra-

mid and verapamil. He had a normal echocardiogram, chest x-ray and electrocardiogram. Holter monitoring before and during flecainide treatment did not reveal ventricular arrhythmias. The patient was an alcoholic and had been drinking heavily before the fatal event, which occurred while he was bathing in the sea with a water temperature of 10°C at most. Even though there have been reports of fatal events during cold water immersion,^{14,15} in light of the Cardiac Arrhythmia Suppression Trial,¹⁶ it cannot be precluded that flecainide treatment contributed to the death of this patient. There have been only occasional reports of life-threatening arrhythmias in patients with supraventricular tachycardias and apparently normal left ventricular function.¹⁷ This emphasizes the need for much larger randomized trials to evaluate drugs for proarrhythmic effects at the ventricular level in patients with non-life-threatening supraventricular arrhythmias. However, in a recent consensus statement, the use of flecainide was not discouraged in this group of patients.¹⁸ In 2 patients, it was necessary to reduce the dosage with disappearance of symptoms. In comparison, in a recent review of reports totaling 695 patients, worsened arrhythmias were reported in 4%, conduction disturbances in 2.2% and heart failure in 0.7%. Noncardiac complaints were reported in 19%.¹⁹

Study limitations: The minielectrocardiogram event recorders were used to evaluate symptomatic attacks of atrial fibrillation and flutter, but it is possible that the patients could have had asymptomatic attacks. Evaluation criteria were ≥ 2 objectively verified attacks in each period. Ideally, all patients should have had a minielectrocardiogram event recorder for the whole study period. However, this was not possible.

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Time of Onset of Supraventricular Tachyarrhythmia in Relation to Alcohol Consumption

Markku Kupari, MD, and Pekka Koskinen, MD

It is widely believed but has never been proved that idiopathic supraventricular tachyarrhythmias beginning during or after weekends or winter holidays are frequently alcohol-related ("holiday heart" syndrome). The time of arrhythmia onset was therefore studied in relation to self-reported ethanol consumption and results of a screening test for alcoholism (CAGE questionnaire) in 289 patients aged <65 years admitted for supraventricular tachyarrhythmias. There were 102 patients having an etiologically idiopathic arrhythmia with a known time of onset. Among them, but not among those with disease-related arrhythmias, patients with arrhythmic episodes beginning on Saturdays or on Sundays were more often chronic alcohol abusers (9 of 19, 47%) than either patients with episodes beginning from Mondays through Fridays (18 of 83, 22%; $p = 0.040$) or control subjects from the out-of-hospital population (8 of 66, 12%; $p = 0.002$). In multivariate analysis, the time of arrhythmia onset was related to the CAGE response ($G^2 = 6.0$, $p = 0.014$) but not to the most recent ethanol use. However, the increased frequency of problem drinkers among patients with weekend-onset idiopathic arrhythmias was only relative, and resulted from a decreased number of abstainers and non-problem drinkers. No conspicuous clustering of alcohol-related arrhythmias was seen after New Year's or May Day. Thus, although the present study confirms an association between heavy drinking and idiopathic arrhythmias beginning during weekends, it shows that the question may be of a relative rather than an absolute overrepresentation. The term holiday heart may also be somewhat misleading since no postholiday accumulation of alcohol-related arrhythmias was found.

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Heavy alcohol consumption can contribute to the onset of supraventricular tachyarrhythmia.¹⁻⁴ The term "holiday heart" syndrome has been coined to indicate that alcohol-related arrhythmias cluster around weekends and after festivities such as the Christmas-New Year period.⁵ A captivating designation, it has become popular both colloquially and in scientific communications.^{1,2,6-8} Yet, the underlying idea was not based on any formal prospective or retrospective investigation but on uncontrolled observations made in a small group of alcoholics.^{5,9} Unable to track down more tenable evidence for the holiday heart phenomenon, we studied the relation of the onset of supraventricular tachyarrhythmias to alcohol use in a larger and less selected patient population.

METHODS

Study population: We studied 289 patients (203 men and 86 women) admitted to the emergency ward of our hospital for symptomatic supraventricular tachyarrhythmias and aged <65 years (mean age 50). Between January and October 1985 we studied each patient with new-onset atrial fibrillation ($n = 98$),¹⁰ between January and September 1986 we studied each patient with recurrent atrial fibrillation ($n = 98$),¹¹ and between December 1986 and September 1987 we studied each patient with supraventricular tachyarrhythmia other than atrial fibrillation ($n = 99$: 50 patients with reentry supraventricular tachycardia, 30 with atrial flutter and 19 with paroxysmal atrial tachycardia). The classification of the arrhythmias was based on a 12-lead electrocardiogram taken on admission.¹² The total number of admissions ($n = 295$) was higher than the number of patients because 6 subjects were admitted twice during these studies; only the first admission was included in the present investigation.

Patient evaluation: Each patient was studied by us in the emergency ward, usually within 12 hours of admission. The date and the day of the week the symptoms of the current arrhythmia had begun were questioned and recorded. In subsequent analyses, patients with weekend arrhythmias (beginning on Saturdays or on Sundays) were compared with those having weekday arrhythmias (beginning from Mondays through Fridays). Each arrhythmia was classified as either disease-related or idiopathic on the basis of clinical examination, 12-lead electrocardiogram, chest x-rays, laboratory tests,¹⁰ and results of all previous cardiac studies. In addition, 205 patients underwent a complete echocardi-

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graphic examination¹³ (Irex System III or Toshiba SSH 60A). The diagnostic criteria for the underlying cardiovascular conditions have been specified earlier.¹⁰

The alcoholic drinks consumed each day during the week preceding the arrhythmia were recorded as grams of absolute ethanol and added up to give the total consumption per week. Subsequently, the patients were categorized into 3 groups by their recent ethanol use: (1) 0 g/week, (2) 1 to 210 g/week, and (3) >210 g/week. The last 2 days' (day of arrhythmia onset and the preceding day) consumption was calculated separately and classified as either small to moderate (≤ 150 g) or large (>150 g). To screen for alcohol abuse, the patients were given the 4 CAGE questions¹⁴⁻¹⁶: Have you ever felt you should Cut down on your drinking? Have people Annoyed you by criticizing your drinking? Have you ever felt bad or Guilty about your drinking? Have you ever had a drink first thing in the morning to steady your nerves and to get rid of a hangover (Eye-opener)? The patients giving ≥ 2 affirmative responses were classified as chronic heavy drinkers^{15,16}; the rest (with 0 to 1 positive response) were classified as abstainers or non-problem drinkers.

Controlling: For a control group, we studied 66 subjects (44 men and 22 women aged <65 years [mean 49]) from the local out-of-hospital population, picked up for us by the Central Office of Statistics. They underwent the same studies as our patients, including the screening for alcoholism and the assessment of the last week's (preceding our contact) ethanol consumption. Eight had hypertension, 3 had coronary artery disease and 2 had chronic pulmonary disease.

Statistics: Group differences in rates and proportions were analyzed by the Fisher exact test and the Pearson chi-square test. Multivariate analyses were made, separately for idiopathic and disease-related arrhythmias, using log-linear models¹⁷ in 4-way tables of the following variables: time of onset of arrhythmia, amount of recent ethanol consumption, CAGE response and type of arrhythmia. The fit of a model was evaluated by the likelihood ratio chi-square test (G^2). The first model to try consisted of only the main effects of the variables. If the fit was poor, 2-way interactions relevant to the purpose of the present study were added to the model one at a time. The improvement of the fit between any 2 nested models M1 and M2 was tested by comparing the difference $G^2_{M1} - G^2_{M2}$ to the chi-square distribution with $df_{M1} - df_{M2}$ degrees of freedom. The improvement was considered statistically significant at $p < 0.05$.

RESULTS

The arrhythmia was disease-related in 185 patients and idiopathic in 104. The most common underlying conditions in the former group were coronary artery disease ($n = 62$), systemic hypertension ($n = 38$), valvular heart disease ($n = 17$), idiopathic dilated cardiomyopathy ($n = 11$) and hypertrophic cardiomyopathy ($n = 7$). The onset time was uncertain in 25 patients, of whom 23 had a disease-related and 2 an idiopathic arrhythmia. All subsequent analyses pertaining to the time of

TABLE I Recent Ethanol Consumption and Response to the CAGE Questionnaire in 66 Subjects Aged <65 Years and Selected Randomly from Out-of-Hospital Population

	No. of Pts.	%*
Ethanol consumption category (g/week)		
0	19	29
1-210	38	57
>210	9	14
Number of positive CAGE responses		
0-1	58	88
2-4	8	12

* Percentage of the total sample.

onset of arrhythmia are based on data of the remaining 264 patients.

Relation of the time of onset of arrhythmia to recent ethanol use: IDIOPATHIC ARRHYTHMIAS: Figure 1 shows the occurrence of idiopathic arrhythmias over the days of the week and the distribution of the patients into the 3 categories of recent ethanol consumption. Table I gives the ethanol consumption data of the out-of-hospital control subjects. A higher proportion of patients with weekend arrhythmias (18 of 19 [95%]) had drunk alcohol during the last 7 days than of either patients with weekday arrhythmias (54 of 83 [65%], Fisher exact test, $p = 0.011$) or of the control subjects (47 of 66 [72%], Fisher exact test, $p = 0.035$). The frequency of recent drinking in the control group remained the same even if the 13 subjects with cardiorespiratory diseases were excluded (38 of 53 [72%]). The last 2 days' ethanol intake totaled >150 g in 5 of 19 patients (26%) with weekend arrhythmias and in 8 of 83 (10%) with weekday arrhythmias (Fisher exact test, $p = 0.060$).

DISEASE-RELATED ARRHYTHMIAS: Figure 2 shows that among patients with disease-related arrhythmias there was no apparent difference in the frequency of recent ethanol consumption between subjects with weekend-onset episodes and those with weekday episodes (29 of 46 [63%] vs 67 of 116 [57%]; Fisher exact test, $p = 0.597$). The last 2 days' consumption totaled >150 g in

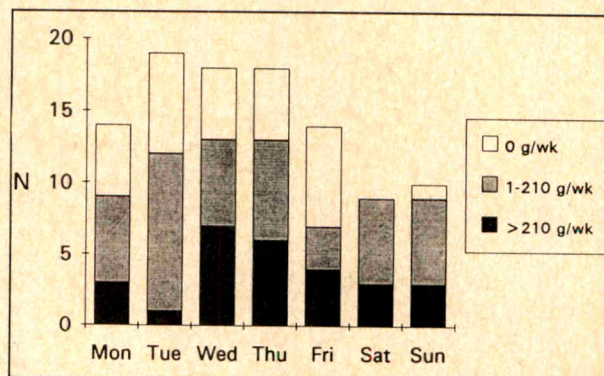


FIGURE 1. The relation between recent alcohol drinking and the day of onset of idiopathic supraventricular tachyarrhythmias. The columns show the number of patients (N) each day of the week and the distribution of the patients into the 3 categories of total ethanol consumption over the preceding 7 days (0 g, 1-120 g, and >210 g).

4 patients from the former group (9%) and in 3 from the latter (3%) (Fisher exact test, $p = 0.101$).

Relation of the time of onset of arrhythmia to the CAGE response: IDIOPATHIC ARRHYTHMIAS: Figure 3 shows that a larger proportion of patients with weekend-onset arrhythmias than of those with weekday episodes responded affirmatively to ≥ 2 CAGE questions (9 of 19 [47%] vs 18 of 83 [22%]; Fisher exact test, $p = 0.040$). However, when the daily arrhythmia rates of problem drinkers were examined, it was found that the number of weekend-onset episodes (9 of the total 27) was not different from the 2 of 7 expected (chi-square = 0.31, $p = 0.578$). By contrast, in non-problem drinkers, only 10 of the 75 arrhythmias had begun during weekends, which was much less than the 2 of 7 expected (chi-square = 9.17, $p = 0.003$). This created a relative overrepresentation of problem drinking among patients with weekend-onset idiopathic arrhythmias.

The CAGE responses of the population controls are summarized in Table I. The frequency of ≥ 2 positive answers was clearly lower than among patients with idiopathic weekend arrhythmias (12 vs 47%; Fisher exact test, $p = 0.002$), but not significantly different from that among patients with weekday arrhythmias (12 vs 22%; Fisher exact test, $p = 0.136$). The frequency of ≥ 2 positive responses among controls free of cardiorespira-

tory disease was 13% (7 of 53 subjects; Fisher exact test, $p = 0.004$ compared with the group of idiopathic weekend arrhythmias).

DISEASE-RELATED ARRHYTHMIAS: Figure 4 shows the frequency of ≥ 2 positive CAGE responses in patients with disease-related arrhythmias. No statistically significant difference was found between subjects with weekend-onset and those with weekday-onset episodes (Fisher exact test, $p = 0.123$).

Relation of recent ethanol use and the CAGE response to the type of arrhythmia (Table II): In assessing whether the type of arrhythmia was alcohol-related, patients with atrial fibrillation ($n = 192$) were compared with those having other supraventricular tachyarrhythmias ($n = 97$). Table II shows that idiopathic atrial fibrillation was more often associated with problem drinking by the CAGE survey than were the other idiopathic arrhythmias. The type of arrhythmia was unrelated to recent ethanol use.

Multivariate analysis: Table III shows the results of log linear modeling for the idiopathic arrhythmias; the factors included and their categories are specified in a footnote to the table. As expected, there was a highly significant relation between recent ethanol consumption and the CAGE response. The time of arrhythmia onset was independently associated with the CAGE response (i.e., adding their interaction to the model improved its fit to the data) but not with the preceding week's ethanol consumption. An association between the type of arrhythmia and the CAGE response was also confirmed. The results were essentially the same even if the last 2 days' ethanol intake (categories: ≤ 150 g, >150 g) was substituted for the whole preceding week's consumption.

In patients with disease-related arrhythmias, the time of arrhythmia onset was associated with neither the CAGE response nor the recent ethanol consumption, and there was no association between the type of arrhythmia and the CAGE response ($p > 0.20$ for each interaction).

Holiday arrhythmias: New Year's and May Day are festivities characterized by alcoholic binges in our country. Over the years 1985 to 1987, only 1 patient was admitted for a supraventricular tachyarrhythmia that had begun during the 3-day period from December 31

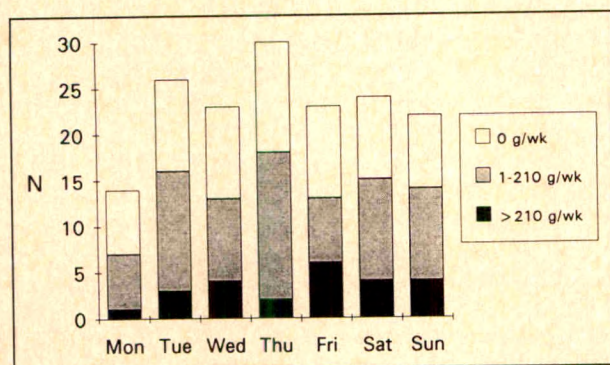


FIGURE 2. The relation between recent alcohol drinking and the day of onset of disease-related supraventricular tachyarrhythmias. For detailed explanation, see the legend to Figure 1.

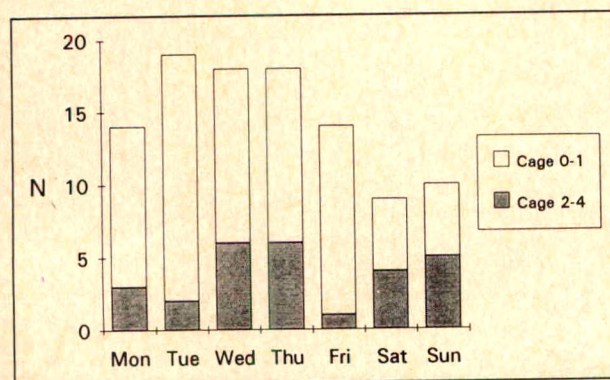


FIGURE 3. The relation between the CAGE questionnaire response and the day of onset of idiopathic supraventricular tachyarrhythmias. The columns show the number (N) of patients each day of the week and their distribution into the 2 CAGE categories (≤ 1 positive response, ≥ 2 positive responses).

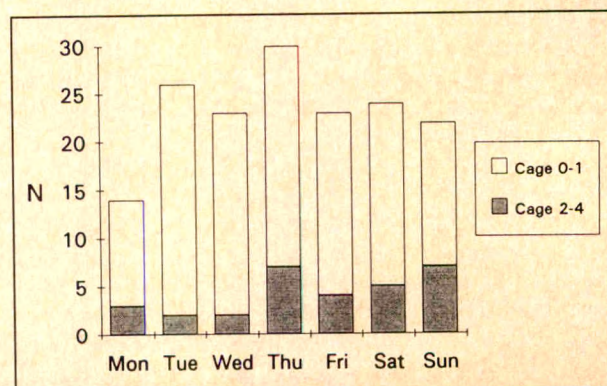


FIGURE 4. The relation between the CAGE questionnaire response and the day of onset of disease-related supraventricular tachyarrhythmias. For detailed explanation, see the legend to Figure 3.

TABLE II Recent Ethanol Consumption and CAGE Questionnaire Response in Relation to Type of Supraventricular Tachyarrhythmia in 289 Patients Aged <65 Years

	Idiopathic Arrhythmias		Disease-Related Arrhythmias	
	AF (n = 59)	non-AF (n = 45)	AF (n = 133)	non-AF (n = 52)
Recent ethanol consumption (g/week)	n (%) [*]	n (%)	n (%)	n (%)
0	16 (27)	14 (31)	52 (39)	23 (44)
1-210	23 (39)	24 (53)	62 (47)	21 (40)
>210	20 (34)	7 (16)	19 (14)	8 (16)
p	0.10		0.74	
Number of positive CAGE responses				
0-1	39 (66)	38 (84)	106 (80)	46 (88)
2-4	20 (34)	7 (16)	27 (20)	6 (12)
p	0.04		0.16	

^{*} The data are given as numbers (percentages) of patients in each category.

AF = atrial fibrillation; p = probability values from comparing the recent ethanol consumption (Pearson's chi-square test) and the CAGE responses (Fisher exact test) between patients with AF and non-AF arrhythmias.

TABLE III Log-Linear Models Showing Independent Relations Among Recent Ethanol Consumption, CAGE Questionnaire Response, Type of Arrhythmia, and Time of Onset of Arrhythmia in 102 Patients Admitted for Idiopathic Supraventricular Tachyarrhythmias

Model	Fit of the Model			Improvement of the Fit		
	G ² *	p	df	G ² Change	p	df
Ethanol + CAGE + time + arrhythmia [†]	83.9	0.000	11			
Ethanol X [‡] CAGE + time + arrhythmia	14.9	0.137	10	69.0	0.000	1
Ethanol X CAGE + time X CAGE + arrhythmia	8.9	0.446	9	6.0	0.014	1
Ethanol X CAGE + time X CAGE + arrhythmia X CAGE	4.0	0.858	8	4.9	0.027	1
Ethanol X CAGE + time X CAGE + arrhythmia X CAGE + time X ethanol	3.4	0.845	7	0.6	0.437	1

^{*} Likelihood ratio chi-square.

[†] The model includes only the main effects of the factors.

[‡] The multiplication sign indicates that both the main effects and the interaction of the 2 factors are effective in the model.

Arrhythmia = the type of arrhythmia in 2 categories (atrial fibrillation, other supraventricular tachyarrhythmia); CAGE = the CAGE questionnaire response in 2 categories (0-1, 2-4 positive answers); df = degrees of freedom; ethanol = the preceding week's ethanol consumption in 2 categories (<210 g, >210 g); p = probability value; time = the time of arrhythmia onset in 2 categories (weekend onset, weekday onset).

through January 2, and 5 patients were admitted for similar arrhythmias beginning from April 30 through May 2. These rates were not higher than the average 3-day frequencies of arrhythmias in January (3.7) or in April and May (3.5). Of the 6 holiday arrhythmias, 5 were idiopathic, but only 1 patient was a problem drinker according to the CAGE response. Five patients had drunk either no ethanol or <150 g over the last 2 days preceding the arrhythmia.

DISCUSSION

The "holiday heart" syndrome was originally defined as "a weekend or holiday presentation of an acute rhythm or conduction disturbance associated with heavy ethanol consumption in a person without clinically evident heart disease and disappearing with abstinence."⁵ The description was based on observations in 24 alcoholics who had a total of 32 hospital admissions with either premature beats or various tachyarrhythmias, mostly atrial fibrillation. Nineteen of the 32 admissions occurred between Sunday and Tuesday, and of the remaining 13 episodes, 6 were seen close to the New Year. The patients did not constitute either a retrospective or a prospective consecutive series, however, and no nonalcoholics with arrhythmias were studied. The fact that several patients had >1 admission included in the study may also have biased the findings, and it is note-

worthy that the time of arrhythmia onset remained unknown since only the day of admission was recorded. For all that, the idea of holiday heart syndrome has survived and become widely accepted.^{1,2,6-8} However, only 1 later study has produced additional data directly pertinent to this phenomenon. In a retrospective case record analysis, Rich et al¹⁸ could not find either postweekend or postholiday accumulation of admissions for alcohol-related atrial fibrillation.

Methodologic considerations: The present study combined 3 separate series of patients admitted for acute symptomatic and sustained supraventricular tachyarrhythmias. During each study period, all patients aged <65 years with similar arrhythmias were included. Any selection bias in the emergency ward, such as was possible in the study by Ettinger et al,^{5,9} was thus avoided. Our hospital is the largest referral center for the city of Helsinki and its vicinities (population 0.9 million), and patients contacting private doctors or community health centers for acute unremitting tachyarrhythmias are as a rule referred to a hospital in our area. However, as we only studied arrhythmias leading to hospital admission, our data may be poorly representative of asymptomatic or nonsustained arrhythmic episodes. Since we, in contradistinction to Ettinger⁵ and Rich¹⁸ and their co-workers, recorded the day of arrhythmia onset instead of the day of admission,

we contrasted Saturdays and Sundays (instead of Sundays, Mondays and Tuesdays) with the remaining days of the week.

In uncovering chronic heavy drinking, we relied on the CAGE questionnaire¹⁴ because it is easy to administer and far superior to conventional laboratory measurements in the detection of alcoholism.^{15,16,19} The score of ≥ 2 positive responses has recently been validated as an index of problem drinking in 2 separate general hospital populations.^{16,19} The limitation of the CAGE survey is that it may not detect the occasional nonalcoholic binge drinker.

Clustering of problem drinkers' idiopathic arrhythmias during weekends — relative rather than absolute: We found that patients who had weekend-onset supraventricular tachyarrhythmias without detectable heart disease were chronic heavy drinkers at least twice as often as patients with similar but weekday-onset arrhythmias. Surprisingly, this did not reflect an increased number of problem drinkers presenting with arrhythmias during weekends but resulted, instead, from a decreased rate of rhythm disturbances in abstainers and non-problem drinkers (Figure 3). The weekend-clustering of alcohol-related arrhythmias was thus apparent rather than real. The possibility that a reduction of alcohol-unrelated arrhythmias during weekends could contribute to or even be the main cause of the holiday heart phenomenon has not been entertained previously. The mechanism of the variation in the occurrence of alcohol-unrelated idiopathic arrhythmias is unknown but could be related, for instance, to a heavier physical or mental (occupational) stress in the middle of the week than on the weekends.

Role of recent ethanol consumption: Although there was a difference between idiopathic weekend and weekday arrhythmias also with respect to the patients' recent use of ethanol, this was neither striking nor independently related to the time of onset of arrhythmia. Recent electrophysiologic studies^{6,7} have shown that alcohol-related arrhythmias result from an interaction of the acute effect of ethanol with the underlying subclinical cardiomyopathy,²⁰ the arrhythmogenic substrate, and that relatively modest acute amounts will do for this. Although the role of excessive binge drinking has thus probably been overemphasized in the past, it certainly is crucial in those rare cases where healthy, nonalcoholic persons have transient hangover-related tachyarrhythmias.²¹

Holiday arrhythmias: During the period of our study, the average New Year sales of alcohol in Finland were 1.9 times higher than the mean sales before ordinary winter weekends, and the respective ratio was 1.6 for the May Day sales compared with spring weekends (unpublished statistics of the Finnish State Alcohol Company). Nevertheless, we did not see any conspicuous accumulation of idiopathic arrhythmias in CAGE-positive persons close to either holiday. Excessive drinking immediately preceding the holiday arrhythmias was not very common either. Although these data speak against postholiday clustering of alcohol-related ar-

rhythmias, they are probably too few to entitle definitive conclusions thereof.

The designation: On the one hand, our data do support the idea of the holiday heart syndrome. The frequency of alcohol abuse among patients with weekend-onset idiopathic arrhythmias was more than double the frequency of abuse in patients with similar but weekday-onset arrhythmias and up to 4 times the prevalence of problem drinking in the out-of-hospital population. On the other hand, the weekend-clustering of problem drinkers' arrhythmias was not absolute, as the original idea indicated,⁵ but resulted from a decreased rate of arrhythmias in abstainers and non-problem drinkers. Neither did we find any particular accumulation of alcohol-related arrhythmias close to New Year's or May Day. Captivating as it is, the designation "holiday heart syndrome" may thus be beside the point, and we think that it would be more appropriate to speak simply of alcohol-related arrhythmias without any epithet. After all, ethanol is the culprit instead of Saturdays, Sundays or holidays.

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Mean and Range of the Ambulatory Pressure in Normotensive Subjects from a Meta-Analysis of 23 Studies

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To perform a meta-analysis of published reports in an attempt to determine the mean and range of normal ambulatory blood pressure (BP), 23 studies including a total of 3,476 normal subjects were reviewed. Most studies were compatible with a mean 24-hour BP in the range of 115 to 120/70 to 75 mm Hg, a mean daytime BP of 120 to 125/75 to 80 mm Hg, and a mean nighttime BP of 105 to 110/60 to 65 mm Hg. With weighting for the number of subjects included in the individual studies, the 24-hour BP averaged 118/72 mm Hg, the daytime BP 123/76 mm Hg, and the nighttime BP 106/64 mm Hg. The night/day pressure ratio averaged 0.87 for systolic and 0.83 for diastolic BP, with ranges across the individual studies from 0.79 to 0.92 and from 0.75 to 0.90, respectively. If the mean \pm 2 standard deviation interval in the various studies was considered normal, the range of normality was on average 97 to 139/57 to 87 mm Hg for the 24-hour BP, 101 to 146/61 to 91 mm Hg for the daytime BP, and 86 to 127/48 to 79 mm Hg for the nighttime BP. Until the results of prospective studies on the relation between the ambulatory BP and the incidence of cardiovascular morbidity and mortality become available, the aforementioned intervals, which summarize the experience of 23 investigators, could serve as a temporary reference for clinical practice.

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Blood pressure (BP) is characterized by a high variability. In addition, the presence of an observer often leads to the overestimation of BP, so-called white coat hypertension. These problems have stimulated the use of noninvasive recorders, which enable repeated BP measurements in ambulatory subjects at programmable intervals during a period of ≥ 24 hours. Despite the potential advantages of ambulatory over casual BP measurements, the clinical relevance of ambulatory readings remains questionable, since there is no agreement among experts on reference values for the diagnosis and treatment of hypertension. The aim of the present study was therefore to review the data at hand, in an attempt to determine the mean and range of ambulatory BP, as reported in normal subjects.

METHODS

Sources of information: English, French and German publications from January 1980 to December 1989 were searched for articles that reported on ambulatory BP in healthy subjects. The articles were retrieved by computer searches using the Medical Literature Analysis and Retrieval System (MEDLARS). In addition, a letter was mailed to participants of an International Consensus Conference on Indirect Ambulatory Blood Pressure Monitoring (Berlin, March 1-3, 1990; Local Organizers: W. Meyer-Sabellek, MD, A. Distler, MD, and R. Gotzen, MD). This letter invited these experts to make their experience with automated ambulatory BP recordings in normal subjects known for inclusion in the present review. Of the 20 letters sent out, 16 (80%) were answered.

Twenty-four articles¹⁻²³ were reviewed. The report by Pagny et al⁷ was not considered as a separate entity in the present analysis, because it was part of a collaborative research project.¹² For all other studies,¹⁻²³ there was no indication that the same subjects were included in >1 report.

Statistical methods: The following information was retrieved from the studies: number of participants, sex and age distribution, technique of ambulatory BP recording, and mean \pm standard deviation of the ambulatory BP for all subjects included in each single study. When the latter was not directly available from published data, they were computed by weighting for the number of subjects included in each of the reported subgroups.

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TABLE I Studies in Normal or Normotensive Subjects

First Author	Year	Subjects	No.	Age (range)	Men (%)	ABP-Method	Day/Nighttime
Pomodossi ¹⁰	88	NT (OBP <140/90)	19	37 (?-?)	74	IA	9-13/0-4 hours
Broadhurst ²⁰	90	Normal (OBP <140/90)	50	44 (18-74)	60	IA	12-18/0-6 hours
Horan ¹	81	NT (OBP <140/90)	21	49 (?-?)	100	A	NA
Pickering ²	82	Healthy volunteers	25	31 (26-43)	76	A	Awake/sleep
Kennedy ³	83	Attendees to health clinic	72	40 (24-69)	100	A	Awake/sleep
Weber ⁵	86	NT (diastolic OBP <90)	29	? (?-?)	100	A	NA
Sundberg ⁸	87	Healthy (OBP <128/90)	9	30 (27-40)	33	A	4-16 hours/sleep
Zachariah ¹⁷	89	Normal subjects	126	49 (20-79)	?	A	NA
Imai ²²	90	NT (community-based)	705	59 (20-?)	32	A	NA
De Gaudemaris ⁶	87	Healthy workers	200	48 (20-59)	48	A(O)	NA
Waring ¹¹	88	NT (mean OBP:135/84)	28	37 (16-76)	54	A(O)	8-22/0-6 hours
Battistella ¹²	89	NT	394	? (20-75)	49	A(O)	9-19/23-7 hours
Chanudet ¹³	89	Healthy subjects	105	21 (?-?)	100	A(O)	6-22/22-6 hours
Chau ¹⁴ *	89	Shift workers	15	30 (25-40)	100	A(O)	9-24/0-9 hours
Harshfield ¹⁵	89	Adolescents recruited via schools, churches	199	13 (9-18)	49	A(O)	Awake/sleep
Enström ²¹	91	NT (diastolic OBP <90)	48	50 (40-64)	100	A(O)	Awake/sleep
Baumgart ¹⁹	90	Normal subjects	152	? (19-71)	51	O	?
O'Brien ²³	91	Bank employees	815	36 (17-65)	49	O	10-20/0-6 hours
Staessen ²⁴	91	Random sample	238	48 (20-79)	47	O	10-20/0-6 hours
Drayer ⁴	85	Healthy (OBP <150/95)	34	38 (20-60)	100	?	6-22/22-6 hours
Pickering ⁹	88	NT	37	31 (?-?)	51	A or A(O)	Awake/sleep
James ¹⁶	89	NT (medical staff)	50	30 (?-?)	0	A or A(O)	Awake/sleep
Meyer-Sabellek ¹⁸	90	NT	105	? (?-?)	57	O or A(O)	?

* Laborers worked on 3 shifts, but only results of the afternoon shifts (noon to 8 P.M.) are included in analysis.

A, O, IA = auscultatory, oscillometric or intraarterial recording; A(O) = auscultatory technique with oscillometric back-up; NA = not applicable; NT = normotensive; OBP = office blood pressure.

In some studies the upper limit of normal was expressed as the ninetieth or ninety-fifth percentile of the data.^{6,23,24} However, since the subjects included in the various studies were not selected on the basis of their ambulatory BP, and since in most studies the ambulatory BP was considered to be normally distributed, the mean \pm 2 standard deviation boundaries were considered to provide an approximate measure of the range of the ambulatory BP in normal subjects. Because the distribution of the ambulatory BP in some reports was slightly skewed to the right, the mean + 3 standard deviations was also computed.

Statistics computed for all studies combined were weighted by the number of subjects included in each single study.

RESULTS

Description of studies: Gender and age of the subjects recruited in the various studies are listed in Table I. Six studies included only male subjects,^{1,3-5,14,15} and 1 report only female subjects.¹⁶ Mean age ranged from 13¹⁵ to 59²² years. One study¹⁵ recruited only adolescents, of whom 54% were black. The smallest study⁸ included 9 persons, and the largest 815.²³

Several techniques were used to record the ambulatory BP: direct intraarterial recordings in 2 studies,^{10,20} an auscultatory method with^{6,11-14,21} or without^{1-4,5,8,22} oscillometric back-up in 12 investigations, and a pure oscillometric technique in 3 studies.^{19,23,24} In studies using a noninvasive technique, the interval between the

BP readings varied from 7.5 minutes^{1,3-5,8} to as long as 30 to 45 minutes.^{9,12,21,23,24}

Most reports presented the mean ambulatory BP during day- and nighttime activities, separately. However, the duration and the timing of the day- and nighttime periods differed slightly from 1 study to the other (Table I). In some studies the day was subdivided in 2 parts, during which the subjects were awake or sleeping, respectively.^{2,3,9,15,16} By contrast, other investigators subdivided the day in 4 parts to eliminate the transition periods between being awake or asleep.^{23,24}

Mean ambulatory blood pressure: Mean systolic and diastolic BP over 24 hours, either reported or computed, were available from a total of 21 studies^{1-6,9-15,17-24} (Figure 1); for these 21 studies combined, they averaged 118 and 72 mm Hg, respectively. In addition, the 95% confidence limits of the individual means indicated that 16 of the 21 reports^{1-6,9-15,17-24} (76%) were compatible with a mean systolic BP over 24 hours of 115 to 120 mm Hg, and 18 (86%) with a mean diastolic BP of 70 to 75 mm Hg.

The mean daytime BP was available in 20 investigations^{2-4,8-24} and the mean nighttime BP was reported in 18 studies.^{2-4,8-16,18-21,23,24} The former averaged 123/76 mm Hg and the latter 106/64 mm Hg. In addition, the 95% confidence limits of the individual daytime means showed that 16 of 20 studies^{2-4,8-24} (80%) were compatible with a mean systolic BP during the day of 120 to 125 mm Hg, and 16 (80%) with a mean daytime diastolic BP of 75 to 80 mm Hg. Furthermore, 11 of 18

studies^{2-4,8-16,18-21,23,24} (61%) were compatible with a mean nighttime systolic BP of 105 to 110 mm Hg, and 12 (67%) with a mean nighttime diastolic BP of 60 to 65 mm Hg.

In the 18 studies,^{2-4,8-16,18-21,23,24} in which ambulatory BP during the day and night were reported separately, the night/day BP ratio averaged 0.87 for systolic and 0.83 for diastolic pressure, with ranges across the studies from 0.79 to 0.92 and from 0.75 to 0.90, respectively.

The influence of gender, age and race on mean blood pressure: In 8 studies,^{6,12,15,18,20,21,23,24} results were reported for men and women separately: With weighting for the number of subjects included in these studies, the 24-hour systolic BP was, on average, 6 mm Hg (range across studies, 3 to 11 mm Hg) higher in men than in women, and the 24-hour diastolic BP 4 mm Hg (0.4 to 9 mm Hg).

Most studies^{1,2,4,5,8-11,13,14,21} did not report on the association or the correlation between the ambulatory pressure and age. However, in the reports,^{3,6,12,22-24} in which the results were presented according to gender and age, the effects of age on systolic BP were different in the 2 sexes. Indeed, in the latter studies,^{3,6,12,22-24} which included a total of 1,105 men and 1,319 women from ages 17 to >80 years, systolic BP increased on average 2.8 mm Hg per decade in women, but only 0.2

mm Hg per decade in men, whereas diastolic BP increased 1.1 mm Hg per decade in men as well as in women.

The influence of age on the ambulatory BP of adolescents was found to be small and not significant when gender and race were accounted for.¹⁵ In the 2 sexes combined, Zachariah et al¹⁷ reported an increase in the 24-hour ambulatory BP, from 122/67 to 125/69 mm Hg from 25 to 75 years. Broadhurst et al²⁰ found a correlation of -0.37 ($p < 0.05$) between age and the mean nighttime BP in men, but not in women, whereas in both sexes the correlations between age and the 24-hour and daytime BP were weak and not statistically significant.

Only few studies reported on the influence of race on the ambulatory BP. Harshfield et al¹⁵ reported that white and black adolescents had the same BP while awake (116/69 vs 116/69 mm Hg). White boys (106 mm Hg), and white (105 mm Hg) and black (105 mm Hg) girls had similar systolic BP during sleep, but black boys had a significantly higher systolic BP (112 mm Hg).¹⁵ Black adolescents, as a group, had significantly higher diastolic BP while asleep than whites (64 vs 61 mm Hg).¹⁵

Normal ambulatory blood pressure: The boundaries corresponding to the mean ± 2 standard deviations and the mean $+ 3$ standard deviations in individual studies

FIGURE 1. Systolic and diastolic blood pressure (BP) over 24 hours in various studies. For each study the following statistics are presented: the mean, the 95% confidence interval of the mean (upper panel), and the mean ± 2 and $+ 3$ standard deviations (lower panel). Abbreviations are used to indicate the technique for BP recording: A = auscultatory; A(O) = auscultatory with oscillometric back-up; IA = intraarterial; O = oscillometric.

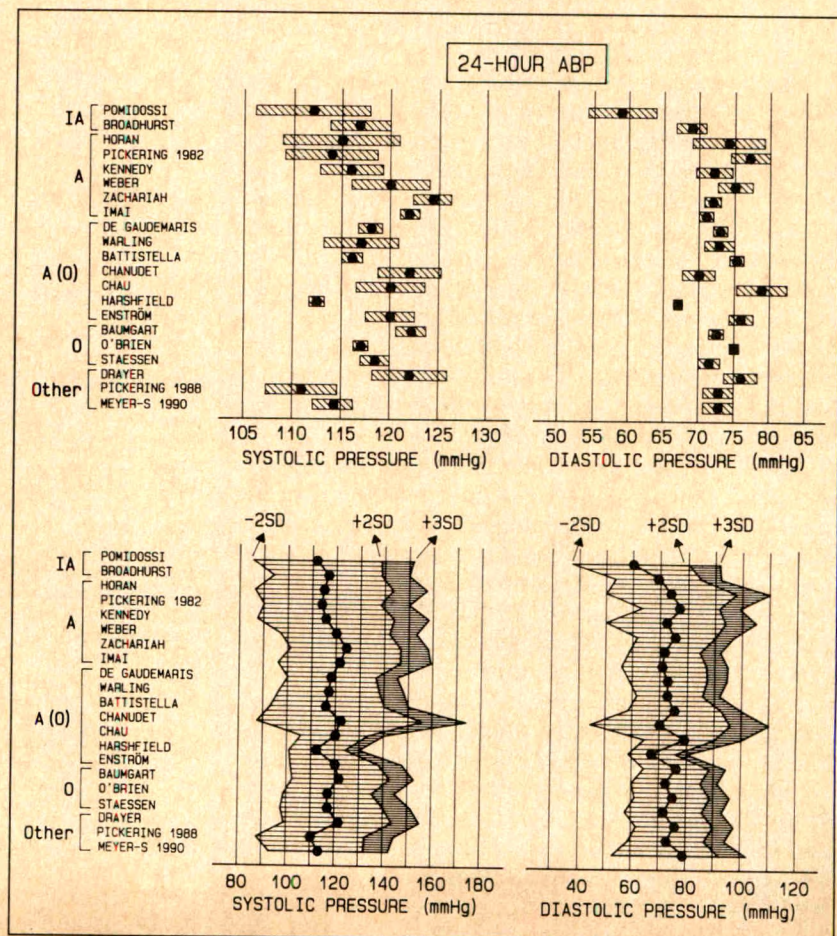


TABLE II Proposal for Reference Values for the Ambulatory Pressure

	24-Hour	Day	Night
Number of studies included in computations	21	19	18
Number of subjects included in computations	3,414	3,226	2,395
Hypotension limit* (mm Hg)	97/57	101/61	86/48
Probable hypertension (mm Hg)	139/87	146/91	127/79
Definite hypertension (mm Hg)	149/94	157/99	137/87

* Reference values were based on the mean \pm 2 standard deviations, and the mean + 3 standard deviations in various studies (see Results for further details).

are shown for 24-hour ambulatory BP in Figure 1. These boundaries for all studies combined, weighted by the number of subjects included in each single study, appear in Table II.

DISCUSSION

The clinical application of ambulatory BP measurements is hampered by the lack of generally accepted reference values. The present meta-analysis suggests that hypertension may be suspected when the 24-hour ambulatory BP is higher than 139/87 mm Hg, or when the day- or nighttime BP exceeds 146/91 or 127/79 mm Hg, respectively (Table II). The limits proposed for the 24-hour and daytime BP approximate the 140/90 mm Hg boundary often used in clinical practice for BP readings obtained by an observer.

Similar to the 140/90 mm Hg upper limit for normotension proposed by the World Health Organization for clinic BP,²⁵ no attempt was made to derive race-, sex- or age-specific reference values. The overall effect of age on ambulatory BP was smaller than expected, especially for systolic BP in men. This may be due to the selection of normotensive subjects across the age strata in various studies. However, also in population studies, in which BP was measured by an observer and in which hypertensive subjects were not excluded, systolic BP increased from 117 to 135 mm Hg in women from 20 to 70 years old, but only from 129 to 138 mm Hg in men of a similar age range.²⁶

Combining the experience of several investigators provides a practical way for estimating the mean and range of the normal ambulatory BP in all published reports. Nevertheless, whether ambulatory BP measurements obtained with different techniques may be pooled remains open for debate. In 1 study,¹⁰ diastolic BP was probably somewhat underestimated because of the insertion of the intraarterial catheter in the distal radial artery, but visual inspection of Figure 1 demonstrates that the use of differing techniques did not produce systematic bias. In addition, the intermittency of noninvasive ambulatory BP measurements up to an interval of 30 to 60 minutes does not preclude an accurate assessment of the true intraarterial BP level.²⁷ Studies with the Remler-recorder were not considered for inclusion in the present meta-analysis, because this technique does not allow the assessment of BP during sleep, and

the muscular activity required for cuff inflation may cause a transient increase in BP.²⁸

Some of the studies listed in Table I recruited industry workers^{6,14} or bank employees.²³ However, in a study that recruited its healthy subjects from a random population sample,²⁴ the ambulatory BP averaged 118/71 mm Hg over 24 hours, 124/76 mm Hg during the day (10 A.M. to 8 P.M.), and 108/62 mm Hg at night (0 A.M. to 6 A.M.). These values are almost identical to the averages obtained for all studies combined in the present meta-analysis. These findings suggest that the reference values presented in Table II and those that will eventually emerge from population surveys will not be much different. Nonetheless, if the limits proposed in the present meta-analysis (Table II) would be applied in clinical practice, their relevance in relation to the incidence of cardiovascular morbidity and mortality needs further clarification.^{29,30}

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Hemodynamic and Neurohormonal Effects of Quinidine in Patients with Severe Left Ventricular Dysfunction Secondary to Coronary Artery Disease or Idiopathic Dilated Cardiomyopathy

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Quinidine causes vasodilation directly and by inhibition of adrenergic vasoconstriction, but it also exerts negative inotropic activity. Although this drug is often administered to patients with severe congestive heart failure, the net consequences of these opposing actions have not been evaluated in such patients. The hemodynamic and neurohormonal response to oral quinidine (600 mg) in 19 patients with severe chronic heart failure was therefore determined. Vasodilation was the predominant effect of quinidine, with reductions in mean arterial, left ventricular filling and right atrial pressures of -9% (confidence interval [CI] -5 to -13), -8% (CI -19 to 3), -15% (CI -26 to -4), respectively. The quinidine-induced vasodilation increased plasma norepinephrine and epinephrine concentrations by 44% (CI +17 to +72) and 47% (CI +2 to +91), respectively. No change in cardiac performance was noted, with the cardiac index slightly increased (+10%, CI +2 to +17) and stroke work index unchanged (0%, CI -11 to +11) after quinidine. Although the mean serum quinidine concentration was within the therapeutic range or lower in all patients, the serum quinidine concentration and the change in mean arterial pressure did correlate ($r^2 = 0.64$). In conclusion, vasodilation is the predominant hemodynamic effect of oral quinidine in patients with congestive heart failure. However, potential adverse effects may be caused by consequent neurohormonal activation.

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Patients with congestive heart failure may exhibit adverse hemodynamic effects when given a medication that causes no such problems in normal persons. For example, we have demonstrated that the administration of antiarrhythmic agents thought to possess minimal negative inotropic activity may cause marked clinical and hemodynamic deterioration when given to a patient with severe left ventricular (LV) dysfunction. Although encainide, tocainide and mexiletine reportedly have minimal hemodynamic consequences in persons with normal cardiac function, we observed marked increases in LV filling pressure and decreases in cardiac output when these agents were given to patients with severe heart failure.¹

There are reasons to suspect that the hemodynamic actions of quinidine could have considerable impact in patients with congestive heart failure, but quinidine's clinical effects are difficult to predict because of its various hemodynamic actions. As with other antiarrhythmic agents, quinidine exerts negative inotropic activity when studied *in vitro*,² but unlike most other antiarrhythmic agents it also is a vasodilator.³ Clinical studies have not noted appreciable hemodynamic effects with quinidine, but this drug has never been studied in patients with severe LV dysfunction using invasive hemodynamic monitoring. This is important information, because patients with heart failure are frequently given quinidine for ventricular or supraventricular arrhythmias. We therefore evaluated the effects of quinidine in patients with severe congestive heart failure using invasive hemodynamic monitoring.

METHODS

Patients: We studied 19 patients with severe LV dysfunction who were referred for the treatment of refractory heart failure. There were 17 men and 2 women aged 34 to 82 years (mean age \pm standard error of the mean 59 ± 3). All patients had a LV ejection fraction $<40\%$ by radionuclide angiography (range 8 to 39% , mean 21 ± 2). The cause of heart failure was coronary artery disease in 8 patients and dilated cardiomyopathy in 11 patients. Thirteen patients were in New York Heart Association functional class III and 6 were in class IV. All patients were receiving constant doses of digitalis and diuretic drugs; previous therapy with vasodilator or antiarrhythmic drugs was withheld for ≥ 24 hours before entry into the study.

Hemodynamic measurements: After written, informed consent was obtained, right-sided cardiac catheterization and arterial cannulation were performed, and patients were permitted to rest overnight to allow for the dissipation of hemodynamic changes related to intravascular instrumentation. On the next morning, after all cardioactive medications were withheld for ≥ 8 hours, the following hemodynamic variables were measured repeatedly in the fasting state until hemodynamic stability was achieved: mean arterial pressure, heart rate, LV filling pressure, mean right atrial pressure and cardiac output, using procedures that have been described previously.⁴

Each patient then received a single oral dose of 600 mg of quinidine, and all hemodynamic variables were reassessed every 15 minutes for 90 minutes after administration of the drug. Seventy-five minutes after the administration of quinidine, blood was collected for the measurement (by fluorescent polarization immunoassay) of serum levels of the drug.

Data analysis: The hemodynamic response to each drug was evaluated by comparing the hemodynamic variables measured after administration of the drug with pretreatment values, using analysis of variance and Fisher's protected least significant difference. Variables measured at the peak effect of the drug (75 minutes after administration) were compared with pretreatment values using the *t* test for paired data. Group data are expressed as mean \pm standard error of the mean. Ninety-five percent confidence intervals (CIs) are given where appropriate.

RESULTS

Hemodynamic response: Vasodilation was the predominant effect of quinidine in these severely ill patients (Table I). The mean systemic vascular resistance and LV filling, right atrial and mean arterial pressures decreased significantly. The mean percent change in these parameters were -14 (CI -5 to -23), -8% (CI -19 to 3), -15% (CI -26 to -4) and -9% (CI -5 to -13), respectively. No change in cardiac performance was noted, with minimal changes in the cardiac index ($+10\%$, CI 2 to 17) and stroke work index (0% , CI -11 to $+11$). The heart rate increased 3% (CI -3 to $+8$).

Serum quinidine concentrations: The mean serum quinidine concentration measured at 75 minutes was 2.2 ± 0.4 $\mu\text{g/ml}$ in the 17 patients in whom it was determined and the level was within the therapeutic range (2 to 6 $\mu\text{g/ml}$) in all patients (Figure 1). Nevertheless, the serum quinidine level and the change in mean arterial pressure did correlate ($r^2 = 0.64$). Similarly, the peak hemodynamic effect occurred at the expected time of peak serum levels (Figure 2). Vasodilation was noted at 30 minutes, and peaked between 75 and 90 minutes.

Catecholamine concentrations: The vasodilation caused by quinidine appeared to initiate an increase in plasma norepinephrine and epinephrine concentrations (Table I), with mean plasma norepinephrine increasing 44% (CI $+17$ to $+72$) and mean plasma epinephrine increasing 47% (CI $+2$ to $+91$). There was a correlation between the change in the mean arterial pressure

TABLE I Hemodynamic Response to Quinidine (600 mg) in 19 Patients with Severe Left Ventricular Dysfunction

	Baseline	Quinidine
Cardiac index (liters/min/m ²)	1.7 ± 0.1	1.9 ± 0.1
Stroke work index (g-m/m ²)	17 ± 2	17 ± 2
Left ventricular filling pressure (mm Hg)	23 ± 2	$20 \pm 2^*$
Right atrial pressure (mm Hg)	11 ± 1	$10 \pm 2^*$
Mean arterial pressure (mm Hg)	86 ± 3	$78 \pm 3^\dagger$
Heart rate (beats/min)	91 ± 4	93 ± 4
Systemic vascular resistance (dynes-cm ⁻⁵)	1912 ± 138	$1586 \pm 93^\dagger$
Plasma norepinephrine (pg/ml)	932 ± 95	$1286 \pm 180^\dagger$
Plasma epinephrine (pg/ml)	111 ± 17	$172 \pm 35^*$

* $p < 0.05$; $^\dagger p < 0.005$.

Mean (\pm SEM) hemodynamic values before and 75 minutes after administration of 600 mg of quinidine.

and the change in the log of the norepinephrine concentration, with $r^2 = 0.57$ (Figure 3).

Clinical response: Two of the 19 patients had symptomatic hypotension with quinidine. One patient became dizzy and diaphoretic at the time of peak hemodynamic effect, when the mean arterial pressure had decreased from 101 to 71 mm Hg. The symptoms and hypotension resolved spontaneously. The second patient experienced nausea coincident with a decrease in mean arterial pressure from 75 to 60 mm Hg 75 minutes after quinidine administration. These symptoms resolved, but 3 hours after quinidine the patient developed ventricular tachycardia necessitating cardioversion. Dyspnea did not increase in any patient with quinidine.

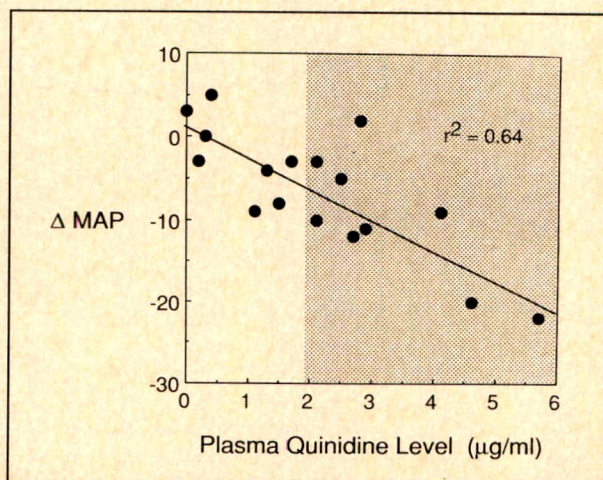


FIGURE 1. The change in mean arterial pressure (ΔMAP , mm Hg) as related to the serum quinidine concentration obtained contemporaneously (75 minutes after quinidine administration). There was a correlation between a decrease in mean arterial pressure and increase in quinidine concentration ($r^2 = 0.64$). All patients had a serum concentration within or below the therapeutic range (shading).

DISCUSSION

This is the first study to evaluate invasively the hemodynamic effects of quinidine in patients with severe heart failure. In contrast to our previous reports of important negative inotropic effects with the administration of other antiarrhythmic agents to patients with severe heart failure, vasodilation was the predominant reaction to quinidine in this study; an adverse effect on LV function could not be discerned.

Vasodilatory effects: The vasodilatory effects of quinidine are well known. As far back as 1948, decreased blood pressure was reported in most patients given a single oral dose of quinidine.⁵ Our findings of marked vasodilation are consistent with previous reports of the hemodynamic actions of quinidine.^{3,6,7}

The extent to which the observed hypotensive effects are secondary to arterial vasodilation or to venodilation is disputed. Some studies report no change in systemic vascular resistance and attribute hypotension to decreased preload,⁸ whereas others report marked decreases in systemic vascular resistance.⁷ In the present study, the marked decrease in systemic vascular resistance reflects maintenance of cardiac output despite a marked reduction in mean arterial pressure and supports the concept that arterial vasodilation caused by quinidine is hemodynamically important.

The venous and arterial vasodilatory effects of quinidine are probably mediated by both a direct action on the vasculature and by inhibition of adrenergic vasocon-

striction. A direct vasodilatory effect is supported by studies demonstrating vasodilation with quinidine in denervated tissues. The importance of the adrenergic system is supported by reports of a decreased vasoconstrictor response to sympathetic nervous stimulation in the presence of quinidine, but this drug had no effect on the response to nonadrenergic vasoconstrictors.^{9,10} The effects of the increased catecholamine concentrations after the administration of quinidine may therefore be largely attenuated; the inability of high catecholamine levels to counteract vasodilation could explain the marked blood pressure response that we observed.

Inotropic effects: The inotropic actions of quinidine have been more controversial than its vasodilator effects. There is evidence both for^{2,3,11,12} and against^{6,9,13} a cardiac depressant effect. Negative inotropy might be expected because of its electrophysiologic actions; quinidine decreases the inward calcium current.¹⁴ However, other ion channels are also affected and could result in an opposite effect. In fact, changes in heart rate may alter quinidine's actions on the different ion channels by varying degrees, and may explain the contradictory inotropic findings of previous studies.¹⁵ Previous studies, using insensitive methods (such as nuclear assessment of ejection fraction and volumes or echocardiographic parameters) to analyze quinidine's actions in patients with heart failure, have suggested a lack of clinically measurable negative inotropic effects.^{16,17} However, such parameters do not reliably indicate the clinical response to a medication.¹⁸ This study, which used invasive hemodynamic monitoring in patients with severe congestive heart failure, strongly indicates that in the clinical setting quinidine should not cause impairment of LV function.

Neurohormonal activation: The increase in catecholamine concentrations seen in our patients was probably not directly caused by quinidine, but rather resulted from the marked hypotension that was observed. Never-

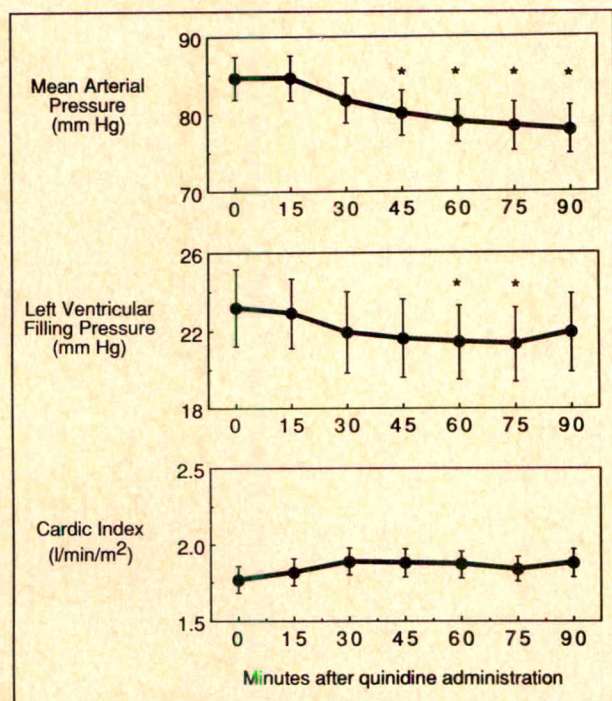


FIGURE 2. Effects of quinidine on mean arterial pressure, left ventricular filling pressure and cardiac index in 19 patients with severe chronic heart failure. Values are shown for each hemodynamic variable at baseline and every 15 minutes (for 90 minutes) after administration of quinidine, expressed as mean \pm standard error of the mean. Asterisk indicates significance ($p < 0.05$) compared with time 0 (before quinidine).

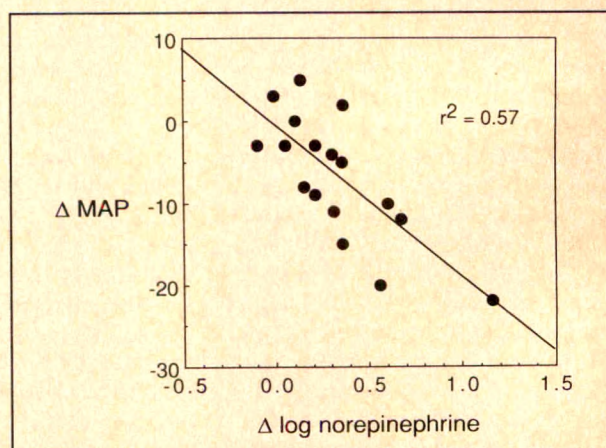


FIGURE 3. The change in mean arterial pressure (ΔMAP , mm Hg) as related to the change in the log of the serum norepinephrine concentration obtained contemporaneously (75 minutes after quinidine administration). There was a correlation between a decrease in mean arterial pressure and an increase in norepinephrine concentration ($r^2 = 0.57$).

theless, the net actions of quinidine may partially depend on the extent of reflex sympathetic activity.¹⁹ Although the catecholamines did not increase heart rate, it is possible that the demonstrated lack of cardiodepressant effect may be partially explained by adrenergic stimulation. Other neurohormonal systems are undoubtedly also activated and may also counteract any negative inotropic actions of quinidine.

Neurohormonal stimulation could also limit the vasodilator effects of quinidine, but only to the extent that quinidine does not interfere with the actions of catecholamines. Quinidine-mediated increases in neurohormonal activity could have adverse consequences, contributing to the paradoxical increase in the frequency of ventricular arrhythmias sometimes seen with quinidine or resulting in a decrease in β -receptor concentration with potential deleterious long-term consequences.

Serum concentrations: The hypotensive response to quinidine was directly related to serum concentrations of the drug. Although all serum quinidine determinations were within or below the usual therapeutic range, this direct relation suggests that vasodilation is not an idiosyncratic response, but an expected consequence of quinidine's mechanism of action. Patients with congestive heart failure may be particularly susceptible to the hypotensive effect of quinidine. First, severe heart failure often leads to low blood pressure, and further reductions could be detrimental. Second, high serum concentrations of normally dosed quinidine may result from the abnormal metabolism of quinidine in patients with LV dysfunction.²⁰ Although careful follow-up can prevent toxic levels of quinidine, this study shows that therapeutic concentrations may also cause hemodynamic alterations.

Study limitations: We attempted to approximate the hemodynamic effects seen during long-term therapy by determining the response to a single loading dose of quinidine. Although higher than the usual initiation dose, administration of 600 mg of quinidine achieved plasma concentrations of the drug similar to those that are associated with an antiarrhythmic effect during long-term therapy.²¹ The importance of the plasma concentration is emphasized by the results of this study. Although hypotension could occur with any serum quinidine concentration, there was a clear relation between the serum level and the hemodynamic effect. Of course, chronic responses to any hemodynamic alteration cannot be determined by a short-term study. For example, it is possible that chronic neurohormonal activation would counter the vasodilation that we observed.

To the extent that any acute study can approximate long-term therapy, this study should reflect the effects of long-term administration of quinidine in patients with severe heart failure. Our findings indicate that the net inotropic impact of initiating quinidine is probably not clinically important. However, the vasodilatory ef-

fects can be significant, and patients with congestive heart failure need to be watched carefully when quinidine is initiated.

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Effects of Prolonged Infusion of Human Alpha Calcitonin Gene-Related Peptide on Hemodynamics, Renal Blood Flow and Hormone Levels in Congestive Heart Failure

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We have previously demonstrated that short-term infusion of calcitonin gene-related peptide (CGRP) has beneficial effects in congestive heart failure. The effects of prolonged infusion of CGRP on hemodynamic functions, plasma hormones and renal blood flow were studied in 9 patients with congestive heart failure (New York Heart Association class III or IV, ejection fraction <35%). Hemodynamic variables were measured at 30-minute intervals for 8 hours during CGRP infusion (8 ng/kg/min) and for 2 hours after discontinuation. CGRP caused a decrease in right atrial (28%, $p < 0.05$), pulmonary artery (22%, $p < 0.02$), pulmonary artery wedge (37%, $p < 0.001$) and systemic arterial (18%, $p < 0.05$) pressures. Systemic vascular resistance decreased more than pulmonary vascular resistance. Cardiac output (72%, $p < 0.001$) and stroke volume (60%, $p < 0.02$) increased. Heart rate did not change. There was no evidence of tolerance throughout the infusion. The hemodynamic effects were lost within 30 minutes of stopping CGRP. Renal blood flow (34%, $p < 0.01$) and glomerular filtration rate (43%, $p < 0.01$) increased. Atrial natriuretic peptide decreased ($p < 0.05$), while plasma cortisol ($p < 0.02$) increased. Plasma epinephrine, norepinephrine, renin activity, aldosterone and growth hormone were unchanged. It is concluded that in patients with severe congestive heart failure, CGRP has sustained beneficial effects on hemodynamic functions and has no adverse effects on hormones. Unlike many other vasodilators, CGRP also increases renal blood flow and glomerular filtration.

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Calcitonin gene-related peptides (CGRP) are alternate products of the calcitonin gene. These recently discovered regulatory neuropeptides are widely distributed in humans and animals,¹ located primarily in the central and peripheral nervous system, the heart and blood vessels.² Relatively large amounts of circulating CGRP are detectable in humans.³ In the heart and blood vessels, specific CGRP-binding sites have been recognized^{4,5} and CGRP has been shown to bind to them. The peptide is one of the most powerful vasodilators known⁶ and in certain species has been shown to have positive inotropic and chronotropic effects.^{3,5,7} Endogenous levels of CGRP are elevated in patients with congestive heart failure, and short-term infusion of CGRP has beneficial cardiovascular effects.⁸ In this study we report the effects of prolonged infusion of this peptide on the hemodynamic functions, renal blood flow and hormone profile in patients with severe chronic congestive heart failure.

METHODS

Patients: The studies were performed in 9 patients (age 52 ± 3 years) with severe chronic congestive heart failure (New York Heart Association class III and IV, ejection fraction <35%). Four patients had coronary artery disease and the remaining 5, idiopathic dilated cardiomyopathy. Three patients had mitral regurgitation (grades I to II) and 1 had tricuspid regurgitation (grade I). The diagnosis was made on the basis of clinical, echocardiographic, hemodynamic and angiographic criteria. Each patient gave written informed consent to the study protocol that was approved by the ethics committee. All patients were taking digoxin and diuretic drugs (average dose of furosemide 160 mg/day). None was receiving vasodilator therapy. Patients were excluded if they had an arrhythmia requiring treatment, unstable angina, recent myocardial infarction or chronic obstructive airway disease.

Protocol: Patients were admitted to the hospital 1 week before the start of the study. Baseline investigations were performed during this period and stability of their clinical status was assessed. A day before CGRP infusion, effective renal plasma flow and glomerular filtration rate were estimated using isotope dilution techniques.⁹ On the next day, studies commenced 2 hours after a light breakfast. After instrumentation, they rest-

TABLE I Effects of Prolonged CGRP Infusion (8.0 ng/kg/min) in Patients with Congestive Heart Failure

	HR (beats/min)	RAP (mm Hg)	PAP (mm Hg)	PAWP (mm Hg)	AoP (mm Hg)	CI (L/min/m ²)	SVI (ml/beat/m ²)	PVR (dynes · s · cm ⁻⁵)	SVR
Basal	98 ± 5	11 ± 2	37 ± 1	24 ± 2	88 ± 5	1.8 ± 0.2	19 ± 2	401 ± 80	2,164 ± 159
During infusion									
30 minutes	100 ± 5	8 ± 2	29 ± 3	16 ± 2	80 ± 4	2.8 ± 0.3	28 ± 3	301 ± 196	1,392 ± 211
2 hours	103 ± 3	8 ± 2	31 ± 3	15 ± 2	75 ± 3	3.0 ± 0.3	29 ± 3	331 ± 106	1,237 ± 203
4 hours	102 ± 5	8 ± 2	31 ± 3	15 ± 2	76 ± 3	3.1 ± 0.4	30 ± 3	396 ± 203	1,200 ± 163
6 hours	102 ± 4	8 ± 1	31 ± 2	17 ± 2	74 ± 3	3.1 ± 0.4	30 ± 3	366 ± 150	1,148 ± 112
8 hours	99 ± 3	9 ± 2	33 ± 1	17 ± 2	73 ± 1	3.0 ± 0.4	30 ± 3	359 ± 144	1,132 ± 114
Infusion discontinued (ID)									
30 minutes	106 ± 4	11 ± 2	38 ± 2	22 ± 3	83 ± 5	2.4 ± 0.5	23 ± 4	497 ± 196	1,664 ± 206
2 hours	106 ± 5	11 ± 2	37 ± 3	22 ± 2	85 ± 3	2.4 ± 0.3	23 ± 3	445 ± 160	1,681 ± 192
Statistics: p values (paired t test)									
Basal vs 30 minutes	0.36	0.02	0.01	<0.001	0.09	<0.001	0.01	0.01	<0.001
Basal vs 8 hours	0.57	0.02	0.06	0.02	0.04	0.01	0.01	0.85	<0.001
4 hours vs 8 hours	0.62	0.85	0.79	0.71	0.95	0.92	0.87	0.64	0.96
8 hours vs 30 minutes ID	0.20	0.15	0.05	0.02	0.03	0.01	0.01	0.05	0.01
Basal vs 30 minutes ID	0.30	0.93	0.71	0.64	0.54	0.24	0.37	0.65	0.10
Basal vs 2 hours ID	0.35	1.00	0.89	0.54	0.63	0.14	0.26	0.82	0.09

Values are expressed as mean ± standard error of the mean.

AoP = mean aortic pressure; CGRP = calcitonin gene-related peptide; CI = cardiac index; HR = heart rate; PAP = mean pulmonary artery pressure; PAWP = pulmonary artery wedge pressure; PVR = pulmonary vascular resistance; RAP = right atrial pressure; SVI = stroke volume index; SVR = systemic vascular resistance.

ed in bed for 1 hour. After baseline hemodynamic measurements were obtained, a blood sample was taken from a peripheral vein for estimating basal hormone levels. Human alpha-CGRP (Celltech Ltd., Berks, United Kingdom) was then infused into a forearm vein using an infusion pump (Harvard apparatus, model 902) at a dose of 8.0 ng/kg/min and was continued for 8 hours. The electrocardiogram and systemic arterial pressure were monitored continuously during the study. Hemodynamic measurements were obtained at half-hour intervals during the infusion. Measurements of effective renal plasma flow and glomerular filtration rate were begun 2 hours after starting the infusion. A second blood sample for hormone assay was taken at 6 hours into the infusion from a peripheral vein in the arm contralateral to that being infused. At the end of 8 hours, the infusion was discontinued while hemodynamic measurements were continued for another 2 hours.

Hemodynamics: Hemodynamic measurements were obtained with a Swan-Ganz catheter placed in the pulmonary artery. Systemic arterial pressure was measured with intraarterial cannulation of the left brachial artery using a 3Fr Teflon catheter (Seldicath). Pressures were measured with Hewlett Packard model 1290C quartz transducers and a Hewlett Packard model 78354A monitor. Cardiac output was determined by thermodilution (SP1445, Gould, Cleveland, Ohio). Hemodynamic variables were derived using standard formulas.

Hormone assay: Hormone assays were performed on a 30-ml blood sample drawn from a forearm vein using methods previously described.^{9,10} Briefly, plasma norepinephrine and epinephrine were measured by high-performance liquid chromatography with electrochemical detection. Plasma renin activity, atrial natriuretic peptide, aldosterone, cortisol, prolactin and growth hormone were measured by radioimmunoassay. Plasma concentrations of CGRP were measured by a nonequi-

librium radioimmunoassay with a standard range curve of 2.5 to 250 pg/ml using a commercial kit (Immunotechnology Service Production). Analytical recovery of synthetic CGRP was 67%. The assay sensitivity was 10 pg/ml.

Effective renal plasma flow and glomerular filtration rate: Effective renal plasma flow and glomerular filtration rate were measured using radioactive isotope of iodine-125-labeled hippuran and chromium-51-labeled ethylenediaminetetraacetic acid, respectively, as described previously.⁹

Statistics: Data are given as mean ± standard error of the mean. The difference in various parameters was estimated by the Student's paired *t* test. A *p* value <0.05 was considered significant.

RESULTS

All patients completed the study without any complications. No patient was allergic to the drug. There was a marked reduction in orthopnea and postural cough during infusion of CGRP. Most patients felt symptomatically better the next morning. Physical signs, however, remained unchanged. No subject complained of flushing or headache during the infusion. The drug did not affect the hematocrit, full blood count or biochemical tests for liver and renal functions. One patient developed slight fever at the fourth hour of infusion due to a pyrogen reaction to intravenous fluids. He completed the study but his data have been excluded from the analysis.

Hemodynamics: Hemodynamic data are given in Table I. CGRP infusion caused a decrease in both the pulmonary (22%, *p* <0.02) and systemic (18%, *p* <0.05) artery pressures. However, systemic vascular resistance decreased to a greater extent (47%, *p* <0.001) than pulmonary vascular resistance (Figure 1). The drug reduced pulmonary arterial wedge (37%, *p* <0.001) and right atrial (28%, *p* <0.05) pressures. Car-

diac output increased 72% ($p < 0.001$) during infusion (Figure 2). Heart rate did not change significantly and stroke volume increased 60% ($p < 0.02$). All hemodynamic changes occurred within minutes of starting the infusion and stabilized by 30 minutes. Thereafter, the effect of the drug was maintained throughout the period of infusion. There was no tolerance in any of the hemodynamic parameters. Hemodynamic variables returned to the basal level within 30 minutes of discontinuing the drug.

Hormones: The hormone data during the study are listed in Table II. Immunoreactive levels of CGRP before infusion were 42 ± 19 pg/ml (normal for our labo-

ratory at 2.5 to 19 pg/ml) and increased to 157 ± 26 pg/ml ($p < 0.01$) when measured at the sixth hour of infusion. Atrial natriuretic peptide levels decreased ($p < 0.05$) while serum cortisol increased ($p < 0.02$). None of the other hormone levels showed any significant change.

Renal blood flow and glomerular filtration rate: Renal blood flow and glomerular filtration rate measured a day before the infusion of CGRP were 129 ± 24 and 51 ± 7 ml/min/1.73 m², respectively. During infusion of CGRP, the renal blood flow increased in every patient and the average increased to 173 ± 23 ml/min/1.73 m², an increase of 34% ($p < 0.01$). Similarly, the

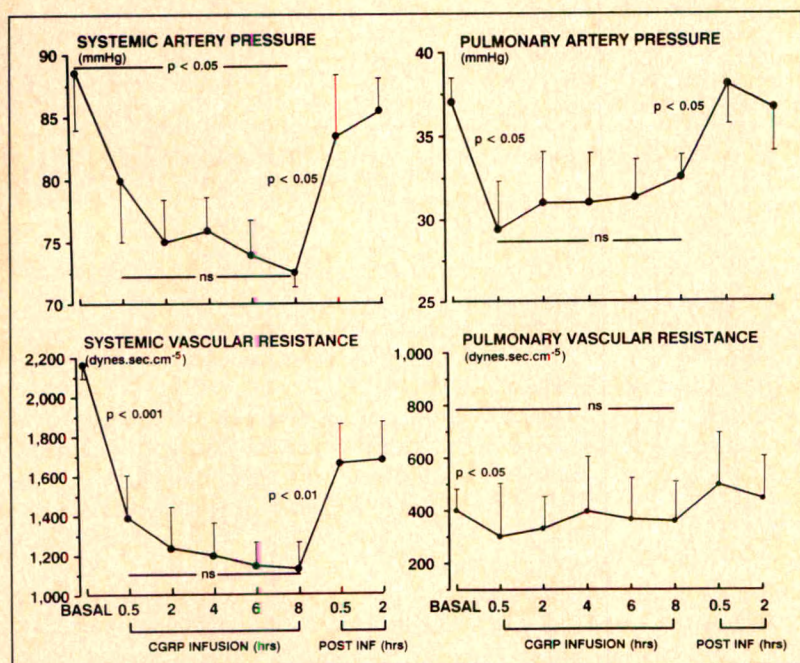


FIGURE 1. Effect of an 8-hour infusion (INF) of calcitonin gene-related peptide (CGRP) on the systemic and pulmonary arterial pressure and resistance in patients with severe congestive heart failure. ns = not significant.

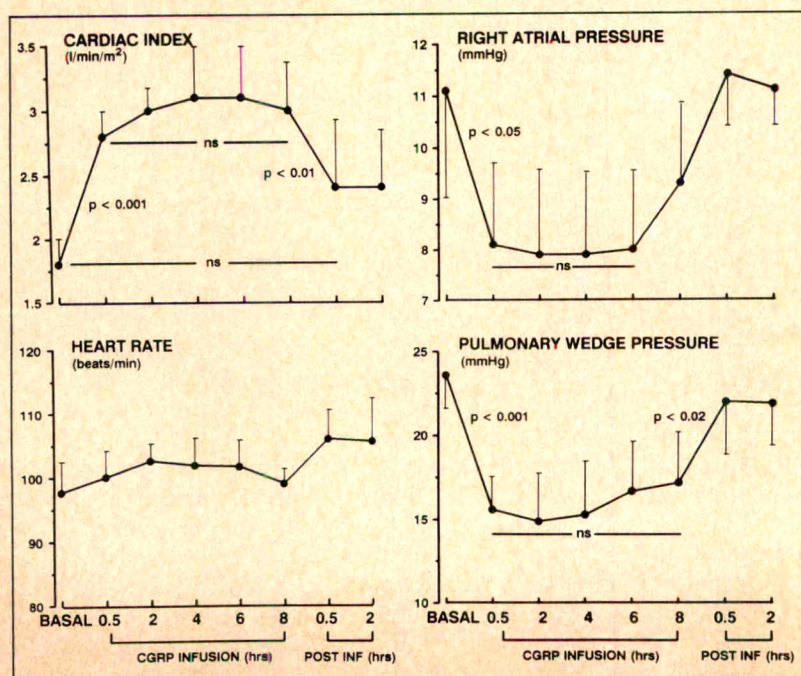


FIGURE 2. Effect of an 8-hour infusion (INF) of calcitonin gene-related peptide (CGRP) on the cardiac output, heart rate and ventricular filling pressures in patients with severe congestive heart failure. ns = not significant.

TABLE II Effect of Infusion of CGRP (8 ng/kg/min) on Hormones in Patients with Congestive Heart Failure

	Basal	Sixth Hour of Infusion	p Value
Epinephrine (pg/ml) (normal limits 0–70)	236 ± 117	197 ± 76	0.47
Norepinephrine (pg/ml) (normal limits 0–370)	1,086 ± 189	1,009 ± 172	0.75
Plasma renin activity (ng/ml/hour) (normal limits 0.2–2.4)	4 ± 2	4 ± 2	0.64
Aldosterone (pg/ml) (normal limits 20–120)	338 ± 138	346 ± 147	0.66
Growth hormone (ng/ml) (normal limits 0.5–6)	3 ± 1	3 ± 1	0.83
Prolactin (ng/ml) (normal limits 5–15)	9 ± 2	8 ± 2	0.78
Cortisol (ng/ml) (normal limits 50–200)	172 ± 25	269 ± 33	0.01
Atrial natriuretic peptide (pg/ml)* (normal limits 9–70)	300 ± 34	247 ± 41	0.03

* n = 7.
Values are expressed as mean ± standard error of the mean.
CGRP = calcitonin gene-related peptide.

glomerular filtration rate increased in all patients, the mean increasing to 72 ± 7 ml/min/1.73 m², an increase of 43% (p < 0.01).

DISCUSSION

We have previously shown that short-term infusion of CGRP in patients with severe congestive cardiac failure caused a dose-dependent increase in cardiac output and a decrease in pulmonary and systemic vascular resistance. At low doses (0.8 and 3.2 ng/kg/min), CGRP behaved as a pure arteriolar vasodilator, whereas at the highest dose (16 ng/kg/min) it was a mixed vasodilator.⁸ In the present study we chose a dose (8 ng/kg/min) midway between the regimens used before. CGRP caused a profound increase in cardiac output, a decrease in ventricular filling pressures, pulmonary and systemic arterial pressures, and vascular resistance. CGRP is also reported to be a potent pulmonary vasodilator.^{8,11} However, in the dose used in this study, although the pulmonary vascular resistance decreased initially, the reduction was not sustained later during the infusion because the pulmonary arterial wedge pressure decreased disproportionately more than the mean pulmonary artery pressure. Similar to our earlier observations,⁸ heart rate did not change throughout the infusion. Tachycardia is frequently seen when CGRP is infused in normal volunteers,^{3,5,7} patients with subarachnoid hemorrhage,¹² and in subjects with Raynaud's syndrome.¹³ The absence of tachycardia in patients with congestive heart failure may be due to a specific effect of this peptide on CGRP receptors in the sinus node.¹⁴ There was no attenuation in hemodynamic response to CGRP during the entire period of infusion, suggesting that at least over an 8-hour period, the drug does not show tolerance. This is consistent with other (short-term) infusion studies.^{3,5,7,12}

Renal blood flow: Renal blood flow is an important factor in the development of the clinical syndrome of congestive heart failure.^{10,15–17} It is a determinant of some important neurohormonal responses¹⁵ and of salt and water retention.^{15,17} Renal blood flow is reduced in

patients with congestive heart failure.^{9,10} CGRP increased renal blood flow and glomerular filtration rate during a reduction in blood pressure. This effect is unlike other vasodilators, where hypotension limits the effect on renal blood flow and natriuresis.^{18,19}

Hormones: Prolonged infusion of the peptide caused a decrease in atrial natriuretic peptide similar to that seen in our acute short-term study⁸ and is probably due to left atrial decompression. CGRP increases norepinephrine levels in normal volunteers^{3,5,7} but did not do so in patients with congestive heart failure. Although norepinephrine is depleted from the nerve endings²⁰ and reflex release of the hormone is blunted in congestive heart failure,²¹ many vasodilators increase plasma catecholamine levels.¹⁸ The findings in our patients could be due to a specific effect of the peptide. Drugs that adversely influence the neurohormonal axis are of little benefit in the long-term management of congestive heart failure.^{15,18,22,23} The lack of deleterious effect on the neurohormonal axis during CGRP infusion may be an advantage.

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Analysis of Survival in Patients with Pulmonic Valve Atresia and Ventricular Septal Defect

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This study reviews the clinical course of 104 consecutive patients with pulmonic valve atresia and ventricular septal (VSD) defect who were diagnosed in the first year of life and followed for a mean period of 4.95 years (range 2 days to 13.75 years). Specific attention was paid to the nature of the pulmonary blood supply and to its influence on patient outcome. Confluent pulmonary arteries supplied by a single ductus arteriosus were present in 72 patients (69%, group I), whereas 32 patients (31%, group II) had a pulmonary blood supply that was partially or exclusively dependent on systemic collateral arteries. An estimate of the probability of survival for 10 years was 69% in the entire cohort, with no difference between patients in group I and group II. Definitive surgical repair was performed in 33 of 72 group I patients (46%), compared with 5 of 32 group II patients (16%). Arborization and distribution abnormalities of the pulmonary arteries as well as intrapulmonary stenoses that were exclusively present in patients with systemic collateral arteries ($p < 0.00001$) accounted for the significantly lower probability of undergoing corrective surgery in group II patients.

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Pulmonic valve atresia with ventricular septal defect (VSD) is an uncommon congenital cardiac anomaly, the prevalence of which is quoted as 0.042 in 1,000 live births.¹ It embraces a wide spectrum of congenitally malformed hearts that have in common the absence of direct flow from the ventricular mass to the pulmonary arteries. Pulmonary blood flow in such patients can be mediated through a number of arterial channels. These could either be a unilateral or bilateral ductus arteriosus, systemic collateral arteries, coronary to pulmonary artery communications, an aortopulmonary window or increased bronchial arterial supply.²⁻¹² Although there are considerable data addressing surgical results in specifically referred cohorts of patients,¹³⁻¹⁹ there are little life-table data available on infants with pulmonary atresia and VSD. This study analyzes survival in a large cohort of patients seen in the first year of life in a single institution. It was also of interest to study the relation between survival and the type of pulmonary arterial blood supply.

DEFINITION

Pulmonic valve atresia with VSD is characterized by a biventricular heart with a large VSD, a single outlet aorta and no direct flow from the ventricles to the pulmonary arteries. The atresia may extend into the pulmonary trunk and into 1 or both central pulmonary arteries. For simplicity, we will summarize these subgroups in the forthcoming text under the term pulmonary atresia. In most cases, the aorta overrides the VSD, but it may be connected preferentially to either ventricle. For this study, we excluded patients with hearts that are functionally or anatomically univentricular and thus require a Fontan-type repair. We included all patients with a biventricular heart, irrespective of whether the atrioventricular connection could be considered concordant or discordant.

The 2 major sources of pulmonary blood supply in pulmonary atresia are the persistent ductus arteriosus and systemic collateral arteries. With few exceptions, any given bronchopulmonary segment will be supplied either by a ductus arteriosus or by systemic collateral arteries, not by both.¹² A ductus arteriosus is defined as a vessel that arises either from the undersurface of the aortic arch or from the base of the innominate artery and joins a central pulmonary artery. Large systemic collateral arteries do not follow the course of the major bronchi and may branch before reaching the hilum. They may have extrapulmonary anastomoses with cen-

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TABLE I Clinical Presentation, Anatomy and Associated Cardiovascular Abnormalities in 104 Patients with Pulmonary Atresia and Ventricular Septal Defect

Patient Characteristics	Group I (n = 32)	Group II (n = 72)
M/F	38/34	20/12
Mean birthweight	2.86 kg	3.02 kg
Median age at first presentation	2 days	8.5 days*
Range	0-302 days	0-281 days
Median age at first palliative operation	3 days	314 days*
Range	1-662 days	5-3,337 days
VSD unrestrictive	70 pts.	32 pts.
Restrictive	2	—
Additional muscular VSD	6	—
Aorta arising		
>50% from left ventricle	4	2
Overriding septum	52	28
>50% from right ventricle	6	2
>90% right ventricle	10	—†
Left aortic arch	56	17
Right aortic arch	16	15†
Aberrant subclavian artery	8	11*
Aortic stenosis	2	3
Aortic regurgitation	1	—
Left coronary-pulmonary artery communication	1	—

Group I = ductal supply of confluent pulmonary arteries.
Group II = pulmonary blood supply by systemic collateral arteries.
* = $p < 0.01$; † = $p < 0.05$; $p > 0.05$ for all other patient characteristics.
VSD = ventricular septal defect.

tral pulmonary arteries or join the pulmonary arteries at the hilar or segmental level. According to their site of origin, they can be classified as direct and indirect aortic branches.²⁰

METHODS

The diagnostic code from the patient data base entered into the computer system of the Division of Cardiology of the Hospital for Sick Children, and cardiovascular surgical and autopsy files were used to identify all patients with pulmonary atresia and VSD who were diagnosed in this institution during the first year of life between January 1, 1976, and December 31, 1988. This time period was chosen because prostaglandin E₂ was introduced to our Hospital in 1975 and prostaglandins were available for treatment in all patients since then.²¹ Patients who were referred from other centers after the first year of life were excluded. We also excluded from consideration 2 children with trisomy 13 and trisomy 18. The follow-up period ended on December 31, 1989.

The diagnosis was confirmed in each patient by echocardiography, cardiac catheterization and angiography, surgery or autopsy findings. At least 1 cardiac catheterization and angiography was performed in 91 patients (88%). In 13 patients (12%), the diagnosis was based on echocardiography and confirmed by autopsy in 4 of them. All the latter patients had a ductal supply of confluent pulmonary arteries. The angiocardiograms were reviewed by ≥ 3 examiners (MH, JTS, PEB, CAFM, RMF). Anatomic detail of the pulmonary circulation was available in 95 of 102 patients.

Assessment of the pulmonary circulation: The diameters of the right and left pulmonary artery were measured angiographically just proximal to the origin of the first branch. As proposed by Shimazaki,¹¹ Kirklin,¹⁵ and their co-workers, the combined diameters of both pulmonary arteries were divided by the diameter of the descending aorta at the level of the diaphragm (the so-called McGoon ratio). Stenoses of the pulmonary arteries were defined as a reduction in diameter of $\geq 50\%$. We distinguished stenoses of the unbranched (proximal to the first branch) and branched portions of the pulmonary arteries. Patients were coded as having intrapulmonary stenosis if ≥ 1 lobe or 3 segments of 1 lung were involved. The pulmonary arteries were considered to have incomplete distribution if ≥ 1 lobe or 3 segments on 1 side were not connected to the hilar portion of the pulmonary arteries.

We divided the patients based on the nature of the pulmonary blood supply. Group I includes all patients with a single ductus supplying confluent pulmonary arteries. Group II comprises patients whose collateral pulmonary blood supply was provided by systemic collateral arteries alone or by a combination of systemic collateral arteries and a ductus arteriosus.

Statistical analysis: The summary of patient characteristics was generated using the means and frequency, *t* test and univariate procedures of the Statistical Analysis System.²²⁻²⁵ A *p* value < 0.05 was considered statistically significant. The SAS Lifetest procedure was applied to generate specific Kaplan-Meier (i.e., product-limit) survival curves.²⁶

RESULTS

Anatomy, associated cardiovascular abnormalities and clinical presentation: One hundred four patients form the study population (Table I). Seven patients (7%) were diagnosed as having atrioventricular discordance (Figure 1). Two of these developed left atrioventricular valve regurgitation because of a dysplastic valve. All 104 patients had a large perimembranous outlet ventricular septal defect. In 2 patients from group I, the VSD became restrictive. Five patients (5%) had aortic stenosis (group I: 2 patients; group II: 3 patients), with gradients ranging from 15 to 80 mm Hg (2 of these have been described previously).²⁷

There was no significant difference in the mean birthweight between patients in group I (mean 2.86 kg) and group II (mean 3.02 kg). The majority of patients in group I presented in the neonatal period for evaluation of moderate or severe cyanosis. Patients in group II had a more heterogenous presentation, with most having only mild cyanosis but signs of congestive heart failure and less frequent moderate to severe cyanosis. This is reflected by a significantly lower median age at presentation for group I patients (2 days) than group II patients (8.5 days, $p = 0.0043$).

The nature of the pulmonary circulation: Confluent pulmonary arteries supplied by a unilateral ductus arteriosus (group I) were present in 72 of the 104 patients (69%). We found a native stenosis of the left pulmonary artery close to the bifurcation in 12, of the right pulmo-

TABLE II Abnormalities of the Pulmonary Vascular Bed (n = 95 patients)

Abnormalities	Ductal Supply of Confluent Pulmonary Arteries (n = 63)	SCA Supply of Pulmonary Arteries (n = 32)
Mean ratio of RPA + LPA/DAO	1.27 ± 0.34*	0.89 ± 0.35† (p = 0.0005)
Stenosis of the unbranched pulmonary arteries	16	2 (p = 0.047)
Left	12	1
Right	3	1
Bilateral	1	—
Stenosis of the intrapulmonary arteries	—	15 (p < 0.00001)
Left	—	5
Right	—	7
Bilateral	—	3
Distribution abnormalities of intrapulmonary arteries	—	22 (p < 0.00001)
Left	—	4
Right	—	5
Bilateral	—	13
Abnormal branching pattern of pulmonary arteries	—	15 (p < 0.00001)
Left	—	5
Right	—	7
Bilateral	—	3

Preoperative measurements of pulmonary artery size based on 32 patients in group I(*) and 18 patients in group II(†).
 DAO = descending aorta; LPA = left pulmonary artery; RPA = right pulmonary artery; SCA = systemic collateral arteries.

nary artery in 3 and bilateral stenoses of the central pulmonary arteries in 1 of the patients in group I (Table II). No patient had stenoses, incomplete distribution or abnormal branching patterns of the intrapulmonary arteries. Preoperative measurements of the diameters of the central pulmonary arteries were available for 32 patients. The mean ratio of the diameters of the right and left pulmonary artery/descending aorta was 1.27 ± 0.34 .

Pulmonary blood supply depended partially or exclusively on systemic collateral arteries in 32 patients (31%) (group II). Measurements of pulmonary artery size were obtained for 18 patients. The size of the group II central pulmonary arteries (expressed again as the

ratio of right and left pulmonary artery/descending aorta) was significantly lower than that of group I (mean 0.89 ± 0.35 , $p = 0.0005$). Angiograms revealed a total of 97 systemic collateral arteries (range 1 to 8, mean 3.06/patient). Ninety systemic collateral arteries originated as direct aortic branches from the descending aorta, whereas the remaining 7 originated as indirect aortic branches. At the time of the first cardiac catheterization, stenoses were present in 54% of the systemic collateral arteries.

Five group II patients had the combination of a unilateral or bilateral ductus with systemic collateral arteries (Figure 1): In 2 patients, a unilateral ductus joined confluent pulmonary arteries; another 2 patients had

FIGURE 1. Pulmonary blood supply in 104 patients with pulmonary atresia and ventricular septal defect. SCA = systemic collateral arteries.

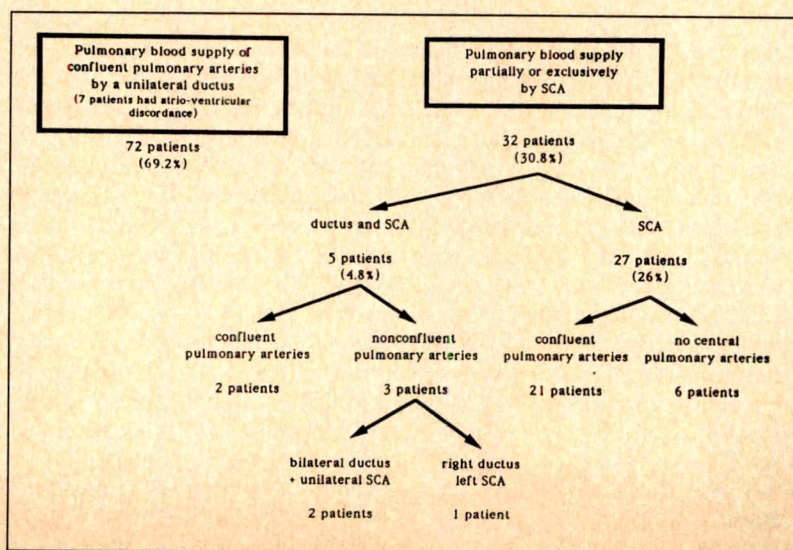


TABLE III Corrective Surgery in 38 Patients with Pulmonary Atresia and Ventricular Septal Defect

	Group I (n = 33)	Group II (n = 5)
Previous palliative surgery		
No operation	1 patient	—
1 operation	15 patients	1 patient
2 operations	14 patients	2 patients
3 operations	3 patients	2 patients
Mean age at corrective surgery (yr)	4.92 ± 1.79	5.53 ± 1.78
Mean body surface area at corrective surgery (m ²)	0.58 ± 0.10	0.61 ± 0.11
Mean postoperative right/left ventricular pressure ratio	0.54 ± 0.16	0.59 ± 0.26
Homograft right ventricle-pulmonary artery	16 patients	3 patients
Allograft right ventricle-pulmonary artery	5 patients 1 death	2 patients
Homograft left ventricle-pulmonary artery	6 patients 1 death	—
Ilbawi procedure	1 patient	—
Right ventricular outflow tract construction	5 patients	—

TABLE IV Present Status of Patients with Pulmonary Atresia and Ventricular Septal Defect

	Group I	Group II	p Value
Dead (%)	20 (27.8)	9 (28)	NS
Corrected and alive (%)	30 (41.6)	4 (13)	p = 0.0034
Awaiting corrective surgery (%)	8 (11.1)	3 (9)	NS
Potential candidate (%)	11 (15.3)	8 (25)	NS
Inoperable (%)	3 (4.2)	8 (25)	p = 0.0014
Total no.	72	32	

NS = difference not significant.

nonconfluent pulmonary arteries supplied by a bilateral ductus, while several segments of 1 lung were perfused separately by systemic collateral arteries; the remaining patient had a ductus supplying the right lung while the left lung was perfused by a systemic collateral artery.

Of the 27 patients who had a collateral pulmonary blood supply provided exclusively by systemic collateral arteries, 21 had confluent pulmonary arteries (78%). In the remaining 6 patients (22%), central pulmonary arteries in the hilar region could not be identified, neither by selective injections in all systemic collateral arteries nor by pulmonary vein wedge angiography.

Abnormalities of the pulmonary circulation were present in a significantly higher number of group II than group I patients ($p < 0.00001$). Unilateral stenoses of the intrapulmonary arteries were present in 38% and bilateral stenoses in 9% of the patients. Twenty-eight percent had unilateral and 41% had bilateral distribution abnormalities of the pulmonary arteries. Abnormal

branching patterns were present in 16% of the patients unilaterally and in 72% bilaterally (Table II).

Outcome in group I: Three patients in this group did not undergo palliative procedures. One patient with Di George syndrome died suddenly in the neonatal period. Another infant who had extremely hypoplastic pulmonary arteries had only a thoracotomy and died at the age of 9 months. A single patient underwent primary repair without prior palliation at age 4.4 years.

At least 1 palliative procedure was performed in 69 patients (96%), 40 patients (56%) required 2 procedures, 9 patients (13%) had 3, and 2 patients (2%) underwent 5 palliative operations. The operative mortality for all 122 palliative procedures was 5%, with 6 deaths among 69 patients (9%). Eight patients (11%) await corrective surgery while another 11 patients (15%) are potential candidates who require recatheterization or another palliative procedure before corrective surgery. Three patients (4%) are no longer candidates for corrective surgery because of acquired intrapulmonary stenoses (2 patients) and acquired atresia of the right (1 patient) or left pulmonary artery (2 patients).

Definitive surgical repair was performed in 33 patients (46%) (Table III). The atretic pulmonary artery segment was replaced by a conduit in 21 patients and by a patch reconstruction of the right ventricular outflow tract in another 5 patients. Six of 7 patients with atrioventricular discordance had a left ventricle to pulmonary artery homograft repair, whereas the remaining patient who had significant left atrioventricular valve regurgitation underwent an Ilbawi procedure (Mustard procedure, intraventricular tunnel from left ventricle to aorta and a right ventricle to pulmonary artery conduit). There were 2 early (6%) and no late deaths.

One patient with atrioventricular discordance died 3 years after a left atrioventricular valve replacement. Four patients underwent conduit replacement at a mean of 3.12 years after the primary procedure without early or late mortality.

In summary, at the end of this study, 20 group I patients were dead (28%), 30 patients were alive after corrective surgery (42%), 19 patients were awaiting corrective surgery (11%) or were considered potential candidates (15%), and 3 patients (4%) were regarded as inoperable (Table IV).

Outcome in group II: Eleven of the 32 group II patients (34%) did not undergo any kind of surgery. The median age at death of the 5 patients who died was 14 days (range 6 to 128 days). The other 6 patients range in age from 1.13 to 7.71 years (mean 4.99) at the conclusion of this study. One of these is a candidate for corrective surgery after successful coil occlusion of several systemic collateral arteries. The remaining 5 children are inoperable because of profoundly hypoplastic (2 patients) or absent central pulmonary arteries (3 patients) in association with arborization and distribution abnormalities of the pulmonary vascular bed, present in all.

Twenty-one of the 32 group II patients underwent ≥1 palliative procedure (66%), 13 patients had 2, and 4 patients had 3 palliative operations. The operative mortality of all 38 procedures was 8%.

Seven patients underwent so-called unifocalization procedures. Five of these had hypoplastic confluent pulmonary arteries, 1 patient had a right-sided ductus and a left pulmonary artery supplied by a systemic collateral artery, and 1 patient had no central pulmonary arteries. Two patients underwent 2 subsequent procedures. In 6 of these 7, the unifocalization procedure was the first palliative procedure to be performed. One child had 2 previous Blalock-Taussig shunts. The procedure most often performed was a modified Blalock-Taussig shunt to the hilar pulmonary artery, with implantation of systemic collateral arteries into the central pulmonary artery (7 procedures/1 death). One patient had a Blalock-Taussig shunt and ligation of systemic collateral arteries. Another patient who did not have central pulmonary arteries underwent implantation of 2 systemic collateral arteries into a conduit from the right ventricle. Of the 6 surviving patients, 1 underwent subsequent corrective surgery (after 2 unifocalization procedures). One patient is suitable for corrective surgery, 1 patient needs further unifocalization, 2 children await restudy and 1 patient is inoperable because of multiple intrapulmonary stenoses.

Of 21 patients with systemic collateral arteries who underwent surgical procedures, 3 died perioperatively (14%). Two patients await corrective surgery, whereas a further 8 patients are potential candidates, requiring either further evaluation, further palliative surgery, or thought to be at an increased risk during future corrective surgery. Three patients are inoperable.

Definitive surgical repair was performed on 5 patients, 4 of whom had confluent pulmonary arteries (Table III). The other patient had nonconfluent central pulmonary arteries that were supplied by a ductus on the left and by a combination of a ductus and 1 systemic collateral artery on the right side. Corrective surgery was performed using a conduit in all cases. There were no early deaths. One patient died suddenly at home, 2 months postoperatively. Another patient underwent successful replacement of an obstructed homograft conduit 3.9 years after the first corrective procedure.

Kaplan-Meier survival curves: The 104 patients were followed for a mean period of 4.95 years (range 2 days to 13.75 years). At the end of the study, 75 pa-

tients (72%) were still alive (Table IV). A total of 29 patients (28%) died. There was no significant difference in mortality between the 2 groups (27.8%, group I vs 28.1%, group II). The median age of death was 275 days with a range of 2 days to 4 years and 11 months. Figure 2 shows the Kaplan-Meier survival curve for all patients with pulmonary atresia and VSD. An estimate of the probability of surviving is 84% for 1 year (95% confidence limits, 77 to 91%) and 69% for 5 and 10 years (95% confidence limits, 59 to 79%). We found no significant difference in survival between patients who had a unilateral ductus supplying confluent pulmonary arteries versus patients who had a pulmonary blood supply provided partially or completely by systemic collateral arteries (Figure 3). Estimated rates of survival in the 2 subgroups were 86 versus 78% after 1 year and 69% in both groups after 5 and 10 years.

DISCUSSION

Reviews of previously published reports by Bertranou,²⁸ Schmaltz,²⁹ and their co-workers revealed that, without surgery, 67 to 78% of patients with pulmonary atresia and VSD die within the first 2 years of life. Because of major improvements in cardiac surgery during the past 2 decades, a considerable number of patients are potential candidates for a biventricular repair.¹⁵⁻¹⁹ Nevertheless, up to now there are no data available either describing the probability of survival based on a large number of unselected patients nor projecting the probability of undergoing a definitive repair. Reliable data concerning the outcome are crucial for counseling parents, especially because it can be expected that a number of patients will be diagnosed prenatally in the near future.

Our study includes 104 consecutive patients who were diagnosed during the first year of life. Because prostaglandin was available for each patient and because cases referred from other centers after the first year of life were excluded, our series represents the first study giving reliable figures on anatomic variations and outcome in patients with pulmonary atresia and VSD.

The results of our study show that patients with pulmonary atresia and VSD have a better overall chance of survival than patients with pulmonary atresia and an

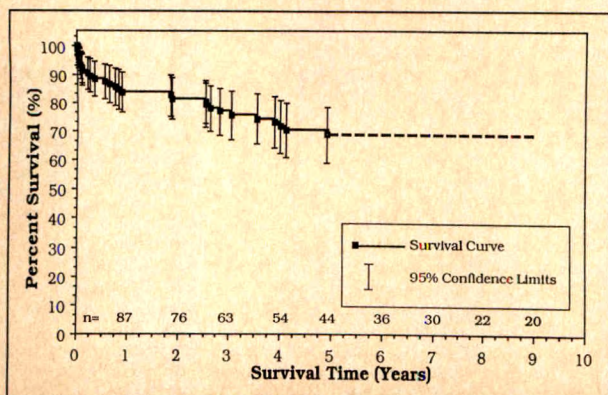


FIGURE 2. Kaplan-Meier survival curve for total cohort of 104 patients with pulmonary atresia and ventricular septal defect.

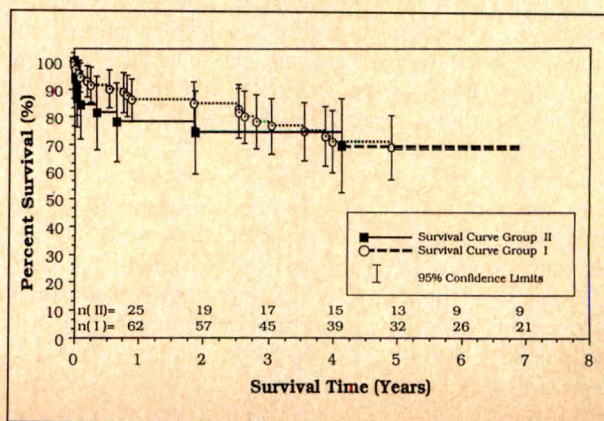


FIGURE 3. Separate Kaplan-Meier survival curves for patients in groups I and II.

intact ventricular septum and patients with tricuspid atresia. The probability of survival at 10 years of age was 69% in children with pulmonary atresia and VSD versus 34% in children with pulmonary atresia and an intact ventricular septum, and versus an estimated 8-year survival of 55% in patients with tricuspid atresia.^{30,31}

The majority of our patients (69%) had confluent pulmonary arteries supplied exclusively by a ductus, 5% had the combination of systemic collateral arteries and a unilateral or bilateral ductus, and 26% had systemic collateral arteries as the single source of pulmonary blood supply. The incidence of systemic collateral arteries was lower in our series, compared with previously reported studies.^{3,8,11,12,32-34} This can be explained by the fact that all previous studies present in some way preselected patient material. This applies specifically to postmortem data from centers that specialize in the surgical treatment of children with complex heart disease.³³ The higher incidence of patients with systemic collateral arteries in previous clinical studies^{3,8,32,34} can be explained by the fact that, at that time, prostaglandin was not available for all patients. Early closure of the ductus arteriosus very likely accounted for a selection in favor of patients with systemic collateral arteries. The presence of systemic collateral arteries is highly associated with abnormalities of the pulmonary vascular bed, such as intrapulmonary distribution abnormalities, intrapulmonary stenoses or abnormal branching patterns.^{4,7,10,11,32,33} Because there are no data up to now projecting the survival rate of such patients in the first decade of life, we compared patients who had a unilateral ductus supplying confluent pulmonary arteries with patients who had ≥ 1 systemic collateral artery. Our analysis reveals that there is neither a significant difference in the probability of survival nor in the operative mortality in the first decade of life between patients who presented originally with a ductus arteriosus alone versus patients with systemic collateral arteries. The estimated rates of survival for 10 years were 69% in both groups. After the first 4 months of life, no child with systemic collateral arteries died deaths unrelated to surgery. Our data suggest that after infancy, patients with pulmonary atresia and VSD have a relatively low risk of death in the first decade of life.

Patients with a ductus-dependent pulmonary circulation have a significantly higher chance of becoming eligible for corrective surgery than patients with systemic collateral arteries (46 vs 16%, $p = 0.0038$). In the former group, only a minor part of patients (4%) was not eligible for corrective surgery versus 25% of patients in the latter group ($p = 0.0014$). We believe this difference between the 2 groups is due to differences in the anatomy of the pulmonary arterial supply and the pulmonary circulation. Patients with systemic collateral arteries had significantly smaller central pulmonary arteries and a significantly higher percentage of arborization and distribution abnormalities, abnormal branching and intrapulmonary stenoses. Patients with a ductus supplying confluent pulmonary arteries more frequently

presented with stenoses of the unbranched portions of the central pulmonary arteries ($p = 0.047$), especially the left. This finding is consistent with data reported by Elzenga and Gittenberger-de-Groot.³⁵ Because these stenoses can be corrected surgically, they usually do not affect the long-term outcome of these patients.

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Pulmonary Artery Morphology and Hemodynamics in Pulmonic Valve Atresia with Ventricular Septal Defect Before and After Repair

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Cardiac catheterization and angiography were performed in 22 patients with pulmonic valve atresia and ventricular septal defect to evaluate pulmonary morphology and hemodynamics before and after repair. In 12 of the 22, pulmonic valve atresia and ventricular septal defect were associated with major aortopulmonary collateral arteries, which were ligated in most. Mean postoperative pulmonary artery pressure (PAP) ranged from 9 to 92 mm Hg (mean 28 ± 19) and pulmonary vascular resistance ranged from 1.1 to 35.2 $\text{U} \cdot \text{m}^2$ (mean 6.4 ± 8.0). These data correlated ($r = 0.89$, $p < 0.001$). The number of pulmonary artery subsegments connected to the central pulmonary arteries was 22 to 42 (mean 38 ± 6). Univariate analysis revealed that the mean postoperative PAP correlated with the number of pulmonary artery subsegments connected to the central pulmonary arteries ($r = -0.81$, $p < 0.001$), with mean preoperative PAP ($r = 0.79$, $p < 0.001$), with the postoperative pulmonary artery area index of the right and left pulmonary arteries at prebranching ($r = -0.76$, $p < 0.001$), and with the sum of the pulmonary artery areas after branching ($r = -0.69$, $p < 0.005$). Pulmonary vascular resistance correlated with the number of pulmonary artery subsegments connected to the central pulmonary arteries ($r = -0.85$, $p < 0.001$), with the mean preoperative PAP ($r = 0.79$, $p < 0.001$), with the sum of the pulmonary artery areas after branching ($r = -0.73$, $p < 0.001$), and with the postoperative pulmonary artery area index ($r = -0.70$, $p < 0.001$). The incidence of pulmonary vascular resistance being $< 3 \text{ U} \cdot \text{m}^2$ was significantly higher in patients with > 36 pulmonary artery subsegments connected to the central pulmonary arteries and with a preoperative pulmonary artery area index > 0.5 (88%) ($p < 0.01$).

These results indicate that postoperative PAP and pulmonary vascular resistance in patients with pulmonic valve atresia and ventricular septal defect may be predictable when the pulmonary artery area at prebranching and the number of pulmonary artery subsegments connected to the central pulmonary arteries are measured before repair. Early palliation to increase pulmonary artery size and the number of pulmonary artery subsegments connected to the central pulmonary arteries is recommended for obtaining normal pulmonary hemodynamics after repair.

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Structures of the pulmonary arteries are abnormal in many patients with tetralogy of Fallot and pulmonary atresia,¹ and postrepair pressure of the right ventricle is high, resulting from stenoses at proximal and distal anastomoses of conduit, conduit obstruction or high pulmonary vascular resistance.^{2,3} Because high pulmonary vascular resistance cannot be reduced, it is important to assess pulmonary vascular resistance in patients with pulmonic valve atresia and ventricular septal defect before surgical repair. Arborization abnormalities, often seen in patients with major aortopulmonary collateral arteries,^{1,4,5} small pulmonary arteries^{5,6} or hypertensive pulmonary vascular obstructive disease may be responsible for increasing pulmonary vascular resistance. In this study, we retrospectively assessed pulmonary artery morphology and hemodynamics in patients with pulmonic valve atresia and ventricular septal defect before and after repair to elucidate factors responsible for increasing pulmonary artery pressure (PAP) and resistance after repair.

METHODS

Patients: Cardiac catheterization and angiographic studies were performed in 22 patients late after repair for pulmonic valve atresia with ventricular septal defect. These patients were recommended for restudy because of suspected conduit obstruction or pulmonary hypertension. Age at the time of surgery was 1 to 20 years (mean \pm standard deviation 8.3 ± 4.6). Ten of the 22 patients had patent ductus arteriosus, and 12 (54.5%) had major aortopulmonary collateral arteries, which

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TABLE I Pre- and Postoperative Hemodynamics and Angiographic Data in 22 Patients

Pt. No.	Age at Repair (yr)	Age at Restudy (yr)	Preop Rp/Rs	PAP (mm Hg)		PAAI		Pp/Ps	No. of Subsegments	PVR (U·m ²)	PVR/ Subsegment	Sum of PA Area (cm ² /m ²)
				Preop	Postop	Preop	Postop					
1	9	10	0.17	(24)	70/11 (34)	0.30	0.61	0.70	31	8.0	248	1.80
2	10	13	0.19	(15)	80/8 (32)	0.27	0.61	0.77	42	5.3	223	1.74
3	16	17	0.12	(33)	65/5 (31)	0.28	0.39	0.52	29	7.2	209	2.21
4	11	12	0.26	(30)	100/12 (46)	0.37	0.38	0.78	35	10.8	378	0.90
5	20	21	0.31	(76)	143/64 (92)	0.40	—	1.25	22	35.2	774	—
6	9	12	0.08	(16)	90/30 (50)	0.22	0.33	0.77	26	20.5	553	1.49
7	8	10	—	—	33/5 (18)	0.60	0.81	0.34	42	1.9	80	2.88
8	5	7	—	(17)	43/16 (30)	0.41	0.68	0.31	33	3.7	122	—
9	1	2	0.30	(48)	36/13 (23)	0.56	0.89	0.41	34	7.6	258	2.50
10	10	14	0.04	(11)	30/9 (16)	0.29	0.50	0.27	40	1.5	60	2.39
11	7	15	0.03	(14)	61/6 (26)	0.26	0.67	0.53	42	3.5	147	—
12	11	12	0.32	(50)	124/14 (52)	0.25	0.25	0.94	34	14.1	465	1.57
13	6	7	0.34	(18)	35/6 (16)	0.59	0.59	0.35	41	2.1	86	3.55
14	7	10	0.17	(24)	38/17 (24)	0.56	0.88	0.33	42	2.8	118	3.43
15	3	12	—	(13)	27/4 (13)	0.72	0.89	0.27	42	2.4	109	3.50
16	6	8	0.08	(9)	38/18 (24)	0.68	0.82	0.41	42	2.1	88	4.47
17	6	7	0.04	(4)	27/8 (14)	0.36	0.76	0.19	42	1.9	80	2.57
18	2	4	0.04	(16)	50/10 (24)	0.56	0.97	0.57	42	3.8	160	4.98
19	10	13	—	(13)	24/4 (12)	0.50	0.78	0.20	42	1.3	50	—
20	15	16	—	—	44/12 (22)	1.03	—	0.39	42	1.1	46	—
21	6	9	—	—	30/4 (15)	0.20	—	0.28	42	2.7	113	—
22	4	6	—	—	18/5 (9)	0.71	0.94	0.19	42	1.5	63	3.55

Numbers in parentheses are mean values.

PA = pulmonary artery; PAAI = pulmonary artery area index; PAP = pulmonary artery pressure; postop = postoperative; Pp/Ps = pulmonary to systemic peak pressure ratio; preop = preoperative; PVR = pulmonary vascular resistance; Rp/Rs = pulmonary to systemic resistance ratio; — = data not available.

were ligated near their origin in 11 patients⁷ and closed by a wire coil in 1. Blalock-Taussig shunts were implanted in 14 patients and a central aortopulmonary shunt in 1. None of the patients underwent unifocalization before repair. Age at the time of restudy was 2 to 21 years (mean 10.8 ± 4.5), and the interval from the repair to restudy was between 7 and 112 months (mean 28 ± 23).

Preoperative study: PAP was obtained through the patent ductus, major aortopulmonary collateral arteries or created shunts in 18 patients. The dimensions of the unbranched hilar portions of the right and left pulmonary arteries were determined preoperatively in all patients. The diameter of the pulmonary arteries was measured at prebranching, unless a discrete stenosis was present more proximally, and then this was measured.⁸ The diameter was converted to the cross-sectional area, and the average of the 2 combined measurements was divided by the mean normal value of the area of the right pulmonary artery, as proposed by Castellanos and Hernandez,⁹ to derive the pulmonary artery area index.

Surgical repair: The repair was performed with a moderately hypothermic cardiopulmonary bypass and, since 1978, with cold crystalloid cardioplegic solution. Surgically created shunts and patent ducti were closed. Discrete stenoses of the central pulmonary arteries were repaired. The ventricular septal defect was closed by right ventriculotomy or through the tricuspid valve. In 20 patients, a valved extracardiac conduit was used to join the right ventricle with the pulmonary arteries. A transannular patch, rather than a valved conduit, was used for the repair in the remaining 2 patients.

Postoperative study: Pulmonary artery wedge pressure was measured, and then that in the pulmonary ar-

tery and right ventricle. No left-to-right shunts were identified by oximetry, and no right-to-left shunts were identified by cineangiography. Cardiac output was determined by the indicator-dilution method, where indocyanine green was injected into the pulmonary artery and samples drawn from the femoral artery. Pulmonary vascular resistance was calculated as $U \cdot m^2$. Pulmonary artery cineangiograms were analyzed in detail, and each of the normal 42 pulmonary artery subsegments¹⁰ and their connection to the central pulmonary arteries was sought. The number of pulmonary artery subsegments connected to the central and unbranched hilar portion of a right and left pulmonary artery was tabulated for each patient. Pulmonary vascular resistance per subsegment was calculated, as well as the total value for the patient. Diameters of the pulmonary arteries were measured, not only at prebranching but also at postbranching of the right and left pulmonary arteries. When there was a discrete stenosis at the pre- and postbranching areas, the stenotic point was measured. There were usually 2 branches in the right pulmonary artery and 2 to 4 branches in the left. Diameters of branches were converted to cross-sectional areas and these were summed to compare the pulmonary artery area index.

Statistical analysis: The observed proportions of discrete events in the 2 groups were compared with chi-square tests. Correlation between 2 variances was considered statistically significant when the p value was <0.05 .

RESULTS

Preoperative data (Table I): The mean PAP ranged from 4 to 76 mm Hg (mean 24 ± 18) in 18 patients and the pulmonary to systemic resistance ratio from 0.03 to

TABLE II Factors Related to Mean Postoperative Pulmonary Artery Pressure

Factor	r	p Value
Number of subsegments connected to the central pulmonary arteries	-0.81	<0.001
Mean preop. PAP	0.79	<0.001
Postop. PAAI	-0.76	<0.001
Sum of PA area after branching	-0.69	<0.005
Age at repair	0.64	<0.02
Preop. PAAI	-0.41	<0.07

Abbreviations as in Table I.

TABLE III Factors Related to Pulmonary Vascular Resistance

Factor	r	p Value
Number of subsegments connected to the central pulmonary arteries	-0.85	<0.001
Mean preop. PAP	0.79	<0.001
Sum of PA area after branching	-0.73	<0.001
Postop. PAAI	-0.70	<0.001
Preop. PAAI	-0.515	<0.02
Preop. Rp/Rs	0.42	<0.2
Age at repair	0.21	<0.4

Abbreviations as in Table I.

0.34 (mean 0.17 ± 0.12) in 15 patients. The pulmonary artery area index ranged from 0.20 to 1.03 (mean 0.46 ± 0.21) in the 22 patients.

Postoperative data (Table I): Systolic PAP ranged from 18 to 143 mm Hg (mean 55 ± 34) and the peak pressure ratio of the pulmonary artery and aorta between 0.19 and 1.25 (mean 0.49 ± 0.28). Mean PAP ranged from 9 to 92 mm Hg (mean 28 ± 19), and was >25 mm Hg in 9 patients. Pulmonary vascular resistance ranged from 1.1 to 35.2 (mean 6.4 ± 8.0) $U \cdot m^2$ and was $>3 U \cdot m^2$ in 11 patients (50%).

The number of pulmonary artery subsegments connected to the central pulmonary arteries was between 22 and 42 (mean 38 ± 6). Only 55% of the patients had all 42 pulmonary artery subsegments connected to the central pulmonary arteries. Pulmonary vascular resistance per subsegment ranged from 46 to 774 $U \cdot m^2$ (mean 201 ± 187). Pulmonary vascular resistance correlated with mean PAP ($r = 0.89$, $p < 0.001$).

The pulmonary artery area index ranged from 0.25 to 0.97 (mean 0.67 ± 0.22) and the sum of the pulmonary artery areas after branching ranged from 0.9 to 5.0 cm^2/m^2 (mean 2.7 ± 1.1). These data correlated ($r = 0.78$, $p < 0.001$).

Factors related to postoperative pulmonary artery pressure: The mean postoperative PAP correlated with the number of pulmonary artery subsegments connected to the central pulmonary arteries ($r = -0.81$, $p < 0.001$), with mean preoperative PAP ($r = 0.79$, $p < 0.001$), with the postoperative pulmonary artery area index ($r = -0.76$, $p < 0.001$), with the sum of the pulmonary artery areas after branching ($r = -0.69$, $p < 0.005$) and with patient age at the time of repair (in years) ($r = 0.64$, $p < 0.02$) (Table II).

TABLE IV Factors Related to Postoperative Pulmonary Artery Area Index

Factor	r	p Value
Sum of PA area after branching	0.78	<0.001
Preop. PAAI	0.77	<0.001
Number of PA subsegments connected to the central pulmonary arteries	0.65	<0.002

Abbreviations as in Table I.

Factors related to postoperative pulmonary vascular resistance: Pulmonary vascular resistance correlated with the number of pulmonary artery subsegments connected to the central pulmonary arteries ($r = -0.85$, $p < 0.001$), with the mean preoperative PAP ($r = 0.79$, $p < 0.001$), with the sum of the pulmonary artery areas after branching ($r = -0.73$, $p < 0.001$), with the postoperative pulmonary artery area index ($r = -0.70$, $p < 0.001$) and with the preoperative pulmonary artery area index ($r = -0.52$, $p < 0.02$) (Table III). Pulmonary vascular resistance per subsegment also inversely correlated with the number of subsegments connected to the central pulmonary arteries ($r = -0.84$, $p < 0.001$).

Factors related to the postoperative pulmonary artery area index: The postoperative pulmonary artery area index correlated with the sum of the pulmonary artery areas after branching ($r = 0.78$, $p < 0.001$), with the preoperative pulmonary artery area index ($r = 0.77$, $p < 0.001$) and with the number of pulmonary artery subsegments connected to the central pulmonary arteries ($r = 0.65$, $p < 0.002$) (Table IV). Moreover, the sum of the pulmonary artery areas after branching correlated with the number of subsegments connected to the central pulmonary arteries ($r = 0.64$, $p < 0.01$).

DISCUSSION

Nearly half the patients had pulmonary hypertension and a high pulmonary vascular resistance. Pulmonary hypertension reflects high right ventricular pressure, which results in poor postoperative status.¹¹ The number of subsegments connected to the central pulmonary arteries was a factor important to the increase in pulmonary vascular resistance, but was not the only one. Pulmonary vascular resistance per subsegment increased as the number of pulmonary artery subsegments connected to the central pulmonary arteries decreased. This study demonstrates that the pulmonary artery was small in patients with a reduced number of pulmonary artery subsegments connected to the central pulmonary arteries and that the postoperative size of the pulmonary arteries was also a factor responsible for increasing pulmonary vascular resistance. The number of subsegments, rather than segments, was used to estimate pulmonary vascular beds in this study. Although pulmonary vascular beds are not identical, even in each subsegment, subsegments may be more appropriate than segments in estimating pulmonary vascular beds.¹²

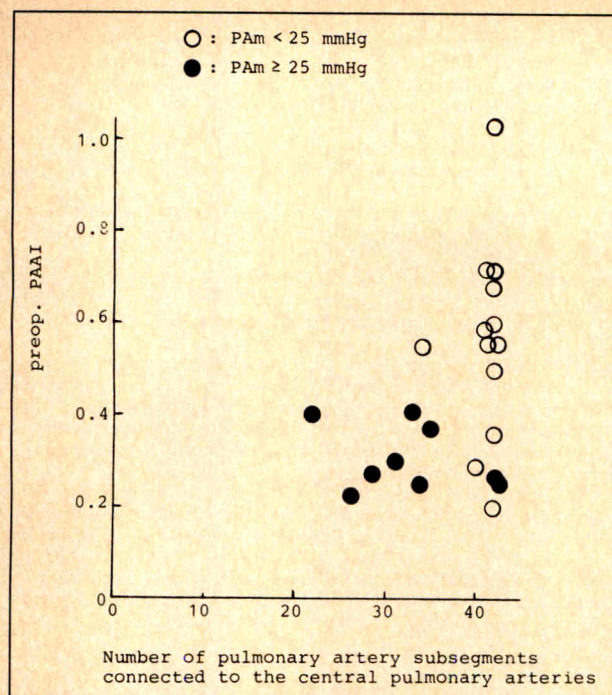


FIGURE 1. Prediction of mean pulmonary artery pressure (PAm) ≥ 25 mm Hg (closed circles) or < 25 mm Hg (open circles) by determination of the relation between the preoperative pulmonary artery area index (preop. PAAI) and the number of pulmonary artery subsegments connected to the central pulmonary arteries. The incidence of mean pulmonary artery pressure being < 25 mm Hg after repair was higher when the pulmonary artery area index was > 0.5 and when the number of pulmonary artery subsegments connected to the central pulmonary arteries was > 36 (100%) ($p < 0.005$).

It is of interest that the postoperative pulmonary artery area index correlated with the sum of the pulmonary artery areas after branching. This suggests that conventional measurement of the size of the pulmonary arteries at prebranching might be appropriate for assuming the size of peripheral pulmonary arteries in patients with this disease, although only sizes of the pulmonary arteries just after branching were measured. The postoperative pulmonary artery area index also correlated with the number of pulmonary artery subsegments connected to the central pulmonary arteries. This indicates that 1 of the abnormalities in the pulmonary vasculature is the smallness of the pulmonary arteries, which reflects pulmonary hemodynamics.

The preoperative pulmonary ratio to systemic resistance ratio was not predictive of an estimated postoperative pulmonary vascular resistance, because pulmonary blood flow included collateral blood flow not passing through the central pulmonary arteries, which affects the calculation of the pulmonary to systemic resistance ratio, and the pulmonary vascular bed was reduced by ligating major aortopulmonary collateral arteries that did not have dual connection. Mean postoperative PAP correlated with mean preoperative PAP; however, the preoperative pressure was not predictive of which patient would have an estimated postoperative pressure < 25 mm Hg late after repair.

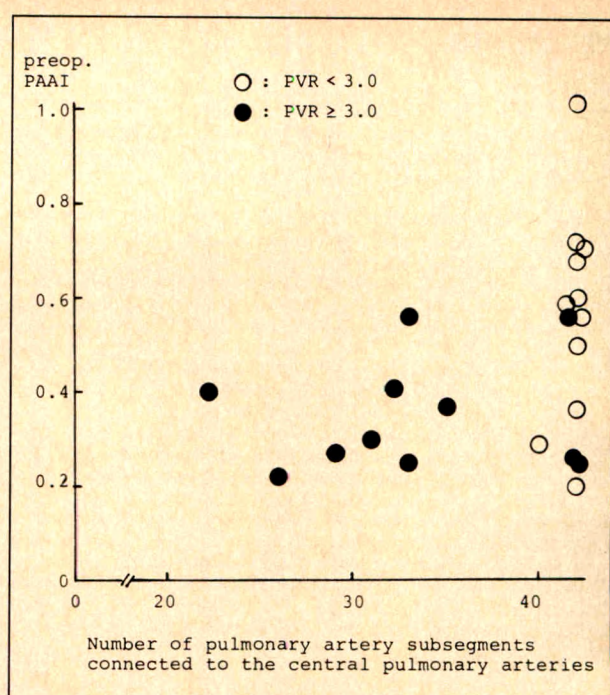


FIGURE 2. Prediction of postoperative pulmonary vascular resistance (PVR) ≥ 3.0 U \cdot m² (closed circles) or < 3.0 U \cdot m² (open circles) by determination of the relation between the preoperative pulmonary artery area index (preop. PAAI) and the number of subsegments connected to the central pulmonary arteries. The incidence of pulmonary vascular resistance being < 3.0 after repair was higher when the pulmonary artery area index was > 0.5 and the number of pulmonary artery subsegments connected to the central pulmonary arteries was > 36 (88%) ($p < 0.05$).

Preoperative prediction of PAP late after repair seems possible when the number of pulmonary artery subsegments connected to the central pulmonary arteries and the pulmonary artery area index are obtained preoperatively. The incidence of mean PAP being < 25 mm Hg, postoperatively, was much higher in patients with a pulmonary artery area index > 0.5 ($p < 0.01$) or in patients with more than 36 pulmonary artery subsegments connected to the central pulmonary arteries ($p < 0.01$) (Figure 1). The incidence of postoperative pulmonary vascular resistance being < 3.0 U \cdot m², where the normal value is 1.54 ± 1.35 (mean ± 2 standard deviations),¹³ was much higher in patients with more than 36 pulmonary artery subsegments connected to the pulmonary arteries and in patients whose preoperative pulmonary artery area index was > 0.50 ($p < 0.01$) (Figure 2).

This study shows that 2 factors are responsible for increasing pulmonary vascular resistance: a reduced number of pulmonary artery subsegments connected to the central pulmonary arteries, and smallness of the pulmonary arteries. Unifocalization¹⁴⁻¹⁶ may help to increase the pulmonary vascular bed. Early palliation is recommended to increase the size of the pulmonary arteries^{5,6} and the number of effective pulmonary artery subsegments necessary to obtain normal pulmonary hemodynamics after repair.

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Catheter-Based Intravascular Ultrasound Imaging of Chronic Thromboembolic Pulmonary Disease

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Pulmonary thromboendarterectomy is now the treatment of choice for pulmonary hypertension due to chronic pulmonary thromboemboli. A precise assessment of location and extension of these thrombi is important because only proximal chronic pulmonary thromboemboli are accessible to surgery. Because intravascular ultrasound imaging can assess not only arterial luminal size, but also wall thickness, its value as a complement to angiography was assessed in 11 patients aged 35 to 64 years with severe pulmonary hypertension (systolic pulmonary artery pressure, mean \pm standard deviation 70 ± 19 mm Hg; pulmonary artery resistance, 609 ± 297 dynes \cdot s \cdot cm⁻⁵). Intravascular ultrasound was obtained in 10 of 11 patients and no complication occurred. Intravascular ultrasound identified 10 segments with suspected chronic pulmonary thromboemboli in 7 patients, all confirmed at operation. Nine segments were considered normal, all of which (except 1) were free of chronic pulmonary thromboemboli at operation. Image quality was highly dependent on pulmonary artery size and position of the catheter. Therefore, intravascular ultrasound of pulmonary arteries is feasible and safe in patients with pulmonary hypertension. It may help to assess the location and extension of the pathologic process involving pulmonary arteries.

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Surgical thromboendarterectomy is now the treatment of choice for severe pulmonary hypertension due to chronic thromboembolic obstruction of the major pulmonary arteries. This operation has been shown to substantially improve pulmonary artery pressure and resistance,¹ cardiac geometry² and functional class.^{1,3} Despite recent advances in surgical techniques, pulmonary thromboendarterectomy still carries a substantial risk with a perioperative mortality of 13% in the most favorable series.⁴ A precise preoperative evaluation of the extent, the location and thickness of the chronic thrombi is essential, therefore, to optimize the surgical result and minimize the operative risks.

Pulmonary angiography is the more reliable diagnostic procedure in these patients, but its interpretation is problematic because of the highly variable pattern of recanalized chronic thromboemboli.^{5,6} Other diagnostic procedures such as angioscopy,⁷ computerized tomography⁸ and magnetic resonance imaging⁹ also have been used to complement pulmonary angiography. Catheter-based intravascular ultrasound is a new technique allowing 2-dimensional, cross-sectional imaging of vessels. It can give information not only on luminal size, but also on vessel wall thickness. Preliminary studies have mostly described its use in vitro and in peripheral arteries.¹⁰⁻¹⁴ Its use in normal pulmonary arteries has also been recently described.¹⁵ In this study, we report our experience with intravascular ultrasound imaging in 11 patients with pulmonary hypertension due to suspected chronic thromboembolic obstruction. Our early findings indicate that intravascular ultrasound can be done safely in these patients and may help to assess the location and extension of the pathologic process involving pulmonary arteries.

METHODS

Patients: Eleven patients (9 men and 2 women aged 35 to 64 years [mean age \pm standard deviation 52.4 ± 10.5]) were evaluated in the University of California, San Diego Medical Center, for pulmonary hypertension and suspected chronic thromboemboli of large pulmonary vessels. All patients underwent thorough clinical assessment and various noninvasive tests including chest x-ray, electrocardiogram, echocardiography, V/Q scan, spirometric testing and arterial blood gas analysis as previously described.^{4,16}

Cardiac catheterization: Before cardiac catheterization, all patients had to be clinically stable, normoten-

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TABLE I Hemodynamic Data in Patients with Suspected Chronic Thromboembolic Pulmonary Hypertension (n = 11)

Pt No.	Systolic PAP (mm Hg)	Mean PAP (mm Hg)	Mean RAP (mm Hg)	Cardiac Output (liters/min)	Pulmonary Resistance (dynes-cm ⁻⁵)
1	85	35	3	5.6	343
2	70	45	14	2.5	1,214
3	74	44	6	4.6	597
4	60	35	6	4.5	515
5	85	58	8	4.1	917
6	80	46	5	5	569
7	85	45	14	3.3	880
8	96	50	7	4.1	702
9	40	23	5	4.5	270
10	38	28	6	2.7	416
11	58	36	9	6.5	283
Mean \pm SD	70 \pm 19	41 \pm 10	7.5 \pm 3.7	4.3 \pm 1.2	609 \pm 297

PAP = pulmonary artery pressure; RAP = right atrial pressure; SD = standard deviation.

sive and free of significant arrhythmias. For access to the right heart, the right internal jugular vein was used to avoid the risk of dislodging thrombi from veins in the legs. After insertion of an 8Fr vascular sheath, a 7Fr thermolubion balloon flotation catheter was advanced to the pulmonary artery to obtain standard measurements of pressures and cardiac output. After completion of the hemodynamic studies, the initial catheter was replaced by an 8Fr Berman catheter. Pulmonary angiograms of the right and the left pulmonary arteries were performed sequentially as previously described.¹⁶

Intravascular ultrasound imaging: A 0.032-inch guidewire was advanced to the pulmonary artery through a 7Fr Critikon balloon catheter. After removal of the catheter, an 8Fr Mullins transeptal sheath was advanced together with the balloon catheter over the wire and left in place to the level of the main right or left pulmonary arteries. The guidewire and the balloon catheter were then removed and the intravascular ultrasound imaging catheter was advanced through the sheath to the right or left main pulmonary artery. A 20-MHz ultrasound imaging system (Cardiovascular Imaging System, Inc., Sunnyvale, California) is mounted on an 8Fr catheter, 65 cm in length. A mechanically rotating mirror located at the tip of the catheter radiates the ultrasound energy and collects the reflecting signals. The signal is then processed to create an image of the artery in a 360° cross-section on a video screen. The penetration of the ultrasound beam using a frequency of 20 MHz is about 1 to 2 cm. The position of the intravascular ultrasound catheter was changed using fluoroscopic guidance. Images were recorded on a videocassette recorder and printed using a Sony UP-100 Videographic Printer. All patients signed an informed consent before the ultrasound procedure, which was approved by the Institutional Review Board at the University of California at San Diego.

Eight patients, 7 with suspected chronic thromboembolic pulmonary hypertension and 1 with suspected pulmonary artery tumor, underwent surgery by techniques previously described.¹⁷ Findings at operation were compared with the location of chronic thromboemboli predicted by intravascular ultrasound.

RESULTS

Hemodynamic findings: All patients evaluated had significant pulmonary hypertension as described in Table I.

Angiographic findings: Pulmonary angiograms were obtained in all patients. The diagnosis of chronic thromboembolic pulmonary hypertension was suspected in 9 of 11 patients. In 1 patient, primary pulmonary hypertension was diagnosed. In another, a primary pulmonary artery tumor was suspected.

Intravascular ultrasound findings: Real time cross-sectional images of the pulmonary arteries were obtained in 10 of 11 patients. In 1 patient, the catheter could not be advanced beyond the right ventricle because an acute angle at that level led to kinking of the sheath. In 3 patients, both right and left pulmonary arteries could be imaged; in 7 patients, only the right pulmonary artery could be imaged while the left pulmonary artery could not be engaged because of an acute angulation at its origin from the main pulmonary artery. The procedure was tolerated well by all patients. No complications occurred.

In the segments considered normal by intravascular ultrasound, the arterial lumen was circular or oval (Figure 1B). Segments with an internal diameter ranging from 6 to 31 mm were imaged. Branches could be detected easily (Figure 2C).

In patients with angiographic suspicion of chronic thromboemboli, 7 had abnormalities on their ultrasound images. In some patients, a marked thickening of the vessel wall was noted (Figure 1C), sometimes with a "crescentic layer" appearance (Figure 2C). In the patient suspected of having a tumor, an echogenic mass was seen adjacent to the vessel wall (Figure 3B). At operation, a fibrous histiocytoma was found extending from the pulmonary valve into the right and left pulmonary arteries.

Correlation with angiographic findings: Ultrasound imaging identified 10 areas in 7 patients that indicated the presence of organized thromboemboli or of tumor. At pulmonary angiography, abnormalities were noted in each instance (Figure 1A). However, in some cases only mild tapering of the vessel was noted (Figure 2A).

Correlation with findings at surgery: Seven of the 8 patients with diagnosis of suspected chronic major vessel thromboembolic obstruction and the 1 with suspected tumor underwent surgery. In 1 patient with suspected thromboemboli, surgery was not undertaken because only mild pulmonary hypertension was present (pulmonary arterial resistance at rest: $280 \text{ dynes} \cdot \text{s} \cdot \text{cm}^{-5}$) and the patient was stable clinically. She was treated by calcium antagonists and will be reevaluated after 6 months. In the surgically treated patients, the diagnosis of chronic thromboembolic obstruction or tumor of pulmonary arteries was confirmed at operation. Chronic organized thromboemboli or tumor were found in each of 10 segments judged abnormal by ultrasound imaging (Figure 4). Nine segments that were judged normal by ultrasound were free of chronic thromboemboli at surgery except 1 case of a clot located in the right proximal pulmonary artery.

DISCUSSION

In this study, we report the initial results of intravascular ultrasound imaging of pulmonary arteries in a unique population with chronic thromboemboli. Our experience indicates that intravascular ultrasound images can be obtained safely and provide information about arterial luminal size and, particularly, vessel wall thickness that cannot be obtained from pulmonary angiograms. Chronic recanalized thromboemboli appear as areas of marked wall thickening or have a crescentic layer appearance. Thus, the technique may serve to localize accurately chronic organized thromboemboli in the pulmonary tree and may help to select the most suitable patients for surgical thromboendarterectomy.

Pulmonary angiography is the most useful method for assessing the extent of chronic pulmonary thromboemboli. However, in many cases, recanalized throm-

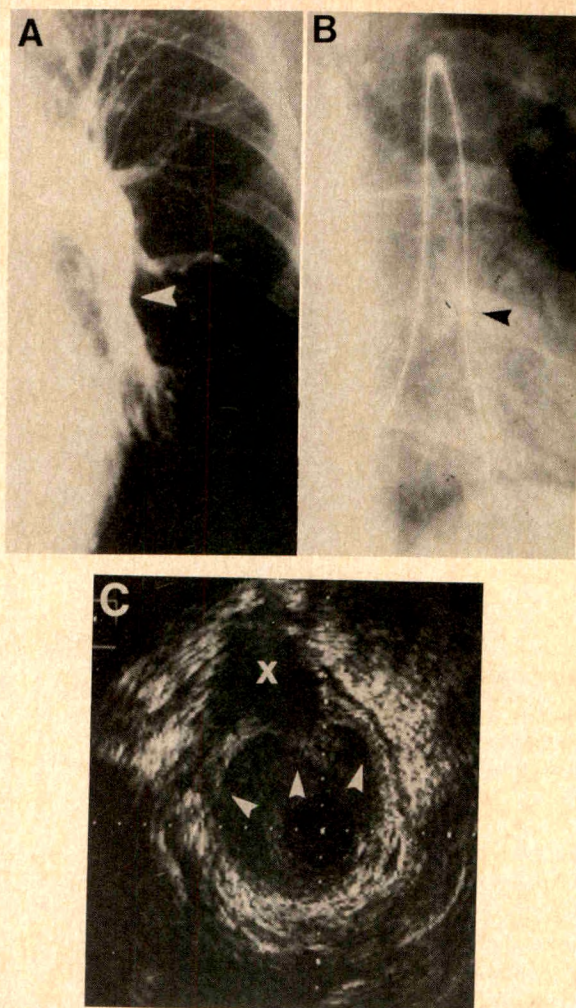


FIGURE 2. *A*, angiographic image of the left pulmonary artery showing a mild tapering of the inferior branch (arrow). *B*, the intravascular ultrasound imaging catheter is positioned in the left inferior lobe pulmonary branch (arrow). *C*, intravascular ultrasound image of the left inferior lobe pulmonary branch showing a "crescentic layer" appearance of the vessel wall (small arrows) (1 mm between dots). X = presence of a side branch.

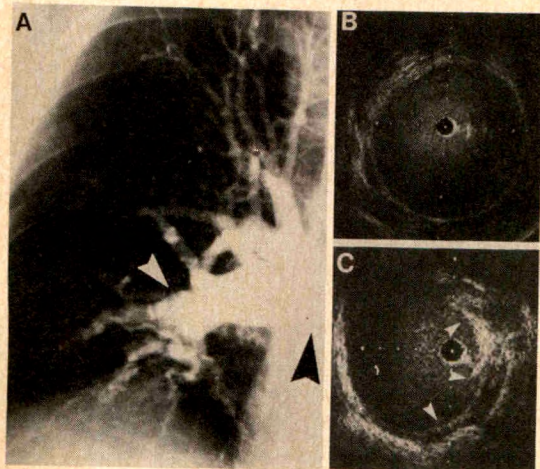


FIGURE 1. *A*, angiographic images of the right pulmonary artery with a normal appearance of the main pulmonary artery (large arrow) and tapering of the inferior lobe branch (small arrow) suggesting chronic clots. *B*, intravascular ultrasound images of the main right pulmonary artery showing a normal appearance of the lumen and of the vessel wall (2 mm between dots). *C*, intravascular ultrasound images of the inferior lobe right pulmonary artery showing thickening of the vessel wall (arrows) (2 mm between dots).

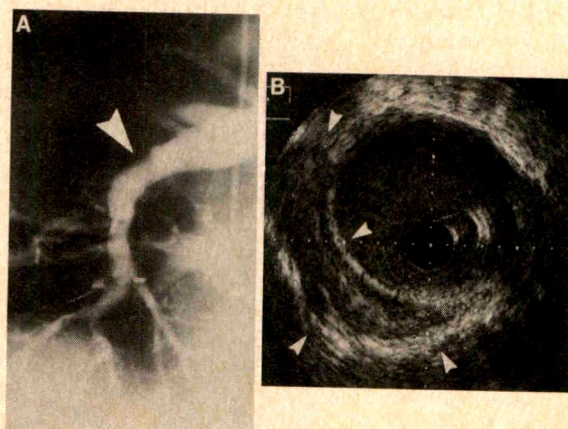


FIGURE 3. *A*, angiographic image of the right pulmonary artery showing a tapering of the intermediate branch (arrow). *B*, intravascular ultrasound image of the intermediate pulmonary artery showing an echolucent mass adjacent to the vessel wall (small arrows) (2 mm between dots). At operation, a fibrous histiocytoma was found.

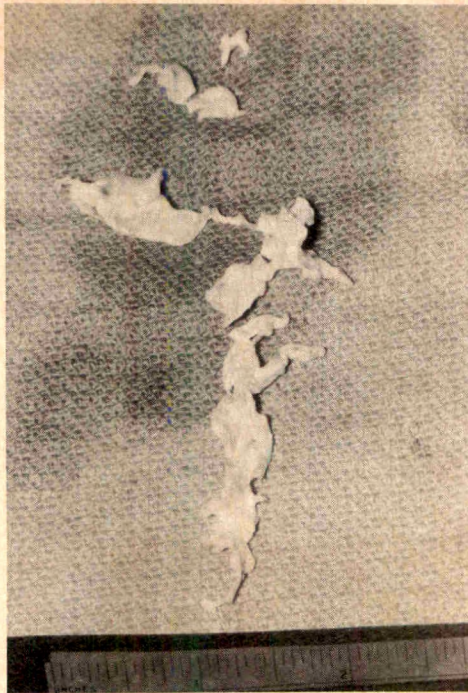


FIGURE 4. Surgical specimen of chronic pulmonary thromboemboli of the right inferior lobe pulmonary branch removed by surgical thromboendarterectomy (same patient as Figure 1).

boemboli are present in areas with only subtle changes on pulmonary angiograms, such as mild or smooth tapering of the artery. This is particularly common when chronic emboli are present in only the lobar or segmental branches and distinct cut-offs or webs are not seen.¹⁸ In such patients, definition of the thickness of the chronic thrombotic material is of particular importance. Even given optimal angiographic/angioscopic information, such distinctions are not possible in some patients. Ultrasound imaging, therefore, could prove valuable in defining the surgical accessibility of these chronic thromboemboli. Identification of tumor masses may also be possible using intravascular ultrasound technology, as suggested by our case of fibrous histiocytoma.

Study limitations: The ultrasound catheter has several important technical limitations. The catheters we have used were stiff and had limited steerability. Imaging was therefore limited to the right and left main pulmonary arteries and descending (lower lobe) lobar arteries. Development of a more flexible over-the-wire system may allow imaging of more distal branches. Also, an over-the-wire system may allow the imaging device to remain in the center of the artery to optimize the quality of the image. Currently, the catheter is often eccentric because of the large size and pulsatility of the pulmonary artery, which results in image distortion and

some loss of information. The ultrasound catheter we used had a frequency of 20 MHz. This allows imaging at a depth of about 1 to 2 cm, which limits visualization of the very large proximal pulmonary arteries often present in this disease. This may explain why we missed a proximal clot in the right pulmonary artery, 28 mm in diameter. The use of catheters with a lower ultrasonic pulse frequency should provide images of larger cross-sectional areas.

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Assessment of Right Ventricular Oxidative Metabolism by Positron Emission Tomography with C-11 Acetate in Aortic Valve Disease

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Evaluation of right ventricular (RV) oxidative metabolism is limited by the inability to easily determine oxygen extraction by the RV myocardium and the complex morphology of this ventricle. Because left ventricular C-11 clearance rate constants closely correlate with myocardial oxygen consumption, it was postulated that C-11 clearance rate constants for the RV free wall should also reflect its oxygen consumption. Therefore, RV C-11 clearance rate constants were compared with RV loading in 21 patients with aortic valve disease to assess the possible use of this technique for noninvasive evaluation of RV oxidative metabolism. RV free wall C-11 clearance rate constants correlated with the product of systolic pulmonary artery pressure and heart rate for all patients ($r = 0.65$, $p = 0.002$), but the relation was stronger if 2 patients with overt RV dysfunction were excluded ($r = 0.83$, $p = 0.001$). On the basis of mean pulmonary artery pressures, patients were stratified into subgroups with normal (group I, $n = 8$) and elevated (group II, $n = 13$) pulmonary pressures and were compared with 10 normal control subjects. RV C-11 clearance rate constants were significantly higher in group II than in group I and in normal control subjects ($p < 0.05$). These data suggest that RV C-11 acetate clearance rate constants can provide noninvasive evaluation of RV oxidative metabolism. This technique may allow serial assessment of RV performance in various cardiac and pulmonary diseases, and particularly of changes associated with therapeutic interventions.

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Impairment of right ventricular (RV) performance can cause significant morbidity in cardiac and pulmonary diseases. Right-sided cardiac catheterization, echocardiography and radionuclide ventriculography provide evaluation of RV loading and function.^{1,2} However, none of these techniques provides direct evaluation of RV oxidative metabolism either globally or regionally. Indeed, oxidative metabolism within the right ventricle has been only poorly characterized because of the inability to measure oxygen extraction by RV myocardium and the complex morphology of the right ventricle, which limits assessment of RV wall stress.³⁻⁸

The RV free wall makes an important contribution to RV performance⁹⁻¹² and may be responsible for maintaining cardiac output in advanced LV dysfunction. Because metabolic demands placed on the RV free wall are influenced significantly by the performance of the ventricular septum,⁶ the ability to directly characterize oxidative metabolism regionally within the right ventricle would have significant advantages.

C-11 acetate has recently been introduced and validated as a tracer of myocardial oxidative metabolism for use in combination with positron emission tomography (PET).¹³⁻¹⁶ We postulated that C-11 acetate clearance rate constants in the RV free wall would reflect its oxygen consumption and correlate with parameters of RV loading in the compensated right ventricle. Consequently, we evaluated the relation between RV C-11 acetate clearance rate constants and RV hemodynamic data in 21 patients with aortic valve disease. The aim of this study was to determine the possible use of this approach for the noninvasive evaluation of RV oxidative metabolism.

METHODS

Patients: The study protocol was approved by the Human Subject Protection Committee of the University of Michigan Medical Center. All normal subjects and patients were studied only after granting informed, written consent.

All 21 patients in the group had aortic valve disease documented by echocardiography and were being electively evaluated for possible aortic valve replacement. This population was chosen because such patients generally have only modest elevation of pulmonary artery pressures and well-preserved RV contractile function.

TABLE I Patient Characteristics

	Group I (n = 8)	Group II (n = 13)
Mean Age \pm SD (years)	61 \pm 16	65 \pm 7
Age range (years)	38–35	50–75
Men:women	6:2	7:6
Primary diagnosis	3 AR, 5 AS	6 AR, 4 AS, 3 mixed

AR = aortic regurgitation; AS = aortic stenosis; mixed = mixed aortic and mitral valve disease; SD = standard deviation.

Eighteen patients had isolated aortic valve disease and 3 patients had mixed mitral and aortic valve disease. All were clinically stable, although 2 had chronic RV failure. None had significant coronary artery disease based on coronary arteriography performed within 1 month of entry into the study. These patients were compared with a group of 9 healthy male volunteers, 22 to 29 years of age (mean \pm standard deviation 26 \pm 3). All volunteers were nonsmokers and were considered to have a low likelihood of coronary artery disease or other cardiac disease based on age, clinical history, physical examination and the presence of a normal electrocardiogram at rest.

Right ventricular hemodynamic data: Right-sided cardiac catheterization was performed for clinical indications in all patients but not in the normal volunteers. RV hemodynamic data were obtained within 1 month of PET and without change in medication in the study interval. Mean, systolic and diastolic pulmonary artery pressures were measured using standard techniques and with the patient lying quietly in the supine position. A RV rate-pressure product was derived by multiplying the systolic pulmonary artery pressure at the time of

right-sided cardiac catheterization by the heart rate recorded at the time of the PET study.

Patients were stratified into subgroups with normal (group I, n = 8) and elevated (group II, n = 13) pulmonary artery pressures based on the recorded mean pulmonary artery pressure. A mean pulmonary artery pressure >20 mm Hg was considered pathologically elevated.¹⁷ The age, sex and clinical characteristics of these subgroups of patients are listed in Table I.

C-11 acetate positron emission tomography: C-11 acetate PET studies were performed using a whole body PET scanner (Siemens 931, CTI, Knoxville, Tennessee), allowing simultaneous imaging of 15 transaxial slices, 6.75 mm in thickness. Transmission images were obtained for 15 minutes and were used for attenuation correction. Dynamic PET imaging was then performed for 31 minutes after intravenous administration of 740 MBq (20 mCi) of C-11 acetate. Ten frames of 90 seconds' duration were obtained, followed by 5 frames of 120 seconds' duration and 2 frames of 180 seconds' duration. C-11 acetate was synthesized using previously described methods.¹³

A single midventricular transverse, transaxial plane in which the right ventricle could be easily identified was chosen for analysis. The decay-corrected, dynamic series of 17 C-11 acetate images for this plane was displayed and regions of interest were assigned on the frame with best myocardial definition (Figure 1A). Regions of interest were assigned for the RV free wall and septum and were then extrapolated to all frames. Monoexponential fitting of the resultant regional time-activity curves was performed after decay correction (Figure 1B). Clearance half-times ($t_{1/2}$) were obtained and C-11 acetate rate constants (k /min) were calculated by dividing the natural logarithm of 2 by the C-11 acetate clearance $t_{1/2}$ in minutes, i.e. $k = \ln 2/t_{1/2}$.¹⁸

Statistical analysis: Values for groups are presented as mean \pm standard deviation. Mean levels of continu-

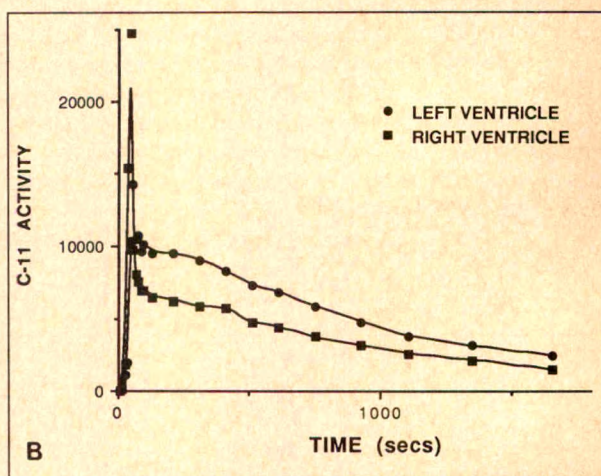
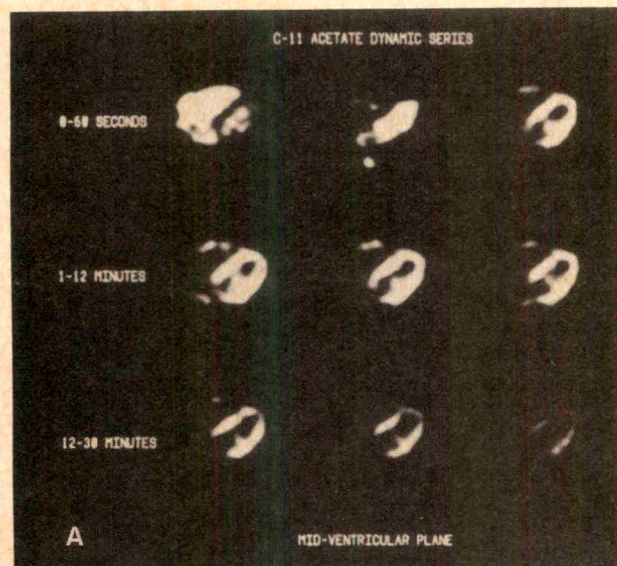


FIGURE 1. A, dynamic series of decay-corrected, C-11 acetate images for a single midventricular, transaxial plane. In the first frame (top left), C-11 activity is mainly in blood. Later, there is rapid and marked blood pool clearance and avid myocardial extraction. By the final frame (bottom right) there has been substantial clearance of myocardial C-11 activity, reflecting metabolism of C-11 acetate via the tricarboxylic acid cycle. B, decay-corrected time-activity curves for right ventricular and left ventricular myocardial regions of interest. Data presented in this figure were derived from analysis of a study done in a patient with elevated pulmonary artery pressures secondary to aortic regurgitation.

ous factors were compared between groups using an unpaired *t* test. RV and septal C-11 acetate clearance rate constants were compared in each patient using a Student's *t* test for paired data. Multiple regression analysis was performed to evaluate the relation between RV hemodynamic data and the RV free wall and septal C-11 acetate clearance rate constants. Pearson's correlations were used to test the association between 2 continuous factors. Probability levels of <0.05 were considered statistically significant.

RESULTS

Comparison of C-11 acetate clearance with right ventricular hemodynamic data: RV C-11 clearance rate constants were significantly correlated with the RV rate-pressure product for all patients (Figure 2A). The 2 patients in this study with overt evidence of RV fail-

ure lay well below the line of identity for this relation. If these patients with RV decompensation and probable impairment of RV contractility were excluded from analysis, a stronger correlation was observed between C-11 clearance in the RV free wall and the RV rate-pressure product ($r = 0.83$, $p = 0.001$) (Figure 2B).

Mean pulmonary artery pressures were significantly higher in the patient subgroup defined as having elevated pulmonary artery pressures (group II) than in the subgroup defined as having normal pulmonary artery pressures (group I) (28 ± 12 vs 13 ± 2 mm Hg, $p < 0.005$, respectively). RV C-11 acetate clearance rate constants were significantly higher in group II than in group I patients ($p < 0.05$) and in normal subjects ($p < 0.005$) (Figure 3). C-11 clearance was faster in patients in group I than in normal subjects without evidence of cardiac disease, although the difference was not statistically significant.

Comparison of right ventricular and septal C-11

clearance kinetics: In patients and in normal volunteers, C-11 acetate clearance rate constants were significantly higher in the septum than in the RV free wall (0.064 ± 0.013 vs 0.043 ± 0.016 , $p = 0.0001$). However, C-11 acetate clearance rate constants in the RV free wall correlated with those in the septum ($r = 0.75$, $p = 0.0001$). Despite this relation, linear regression analysis of C-11 acetate clearance rate constants in the septum versus RV hemodynamic parameters revealed no significant correlation except with heart rate ($r = 0.53$, $p < 0.05$). This was in contrast to the RV free wall C-11 acetate clearance rate constants which correlated significantly with mean pulmonary artery pressure ($r = 0.62$, $p < 0.005$), systolic pulmonary artery pressure ($r = 0.56$, $p < 0.01$), RV rate-pressure product ($r = 0.65$, $p < 0.005$) and heart rate ($r = 0.47$, $p < 0.05$). Multiple regression analysis demonstrated a significant correlation between RV free wall C-11 acetate clearance rate

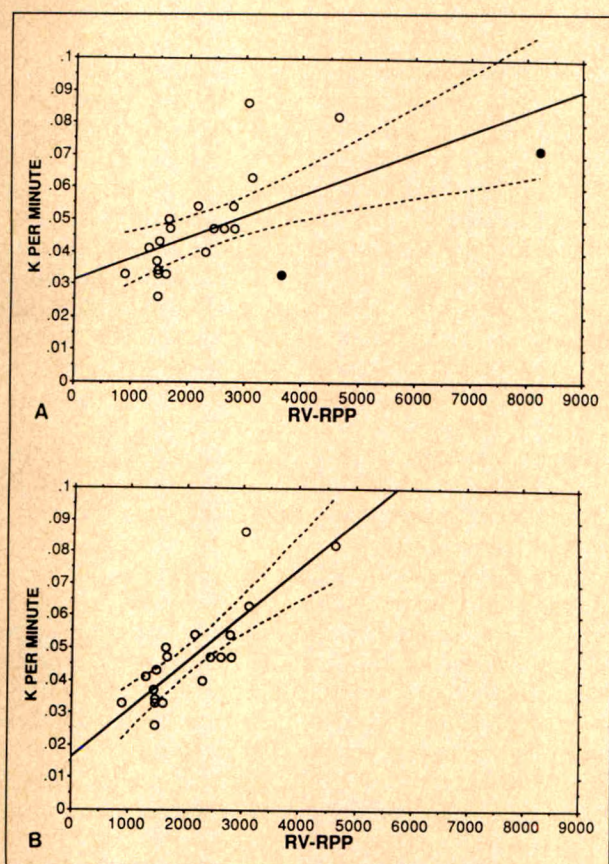


FIGURE 2. A, plot of right ventricular (RV) C-11 clearance rate constants versus the RV rate-pressure product (RPP) calculated by multiplying the systolic pulmonary artery pressure at the time of right-sided cardiac catheterization and heart rate during the positron emission study. A significant correlation was noted ($r = 0.65$, $p = 0.002$). Two patients had overt RV dysfunction (closed circles) included in this regression. The 95% confidence bands of the true mean of acetate rate constants (*k*) per minute are displayed. B, exclusion of the 2 patients with RV dysfunction who likely had impaired contractility made the correlation between these parameters stronger ($r = 0.83$, $p = 0.001$). Again, the 95% confidence bands of the true mean of *k* per minute are displayed. These data suggest that C-11 clearance rate constants are closely related to RV loading in the compensated right ventricle but less well in the failing right ventricle.

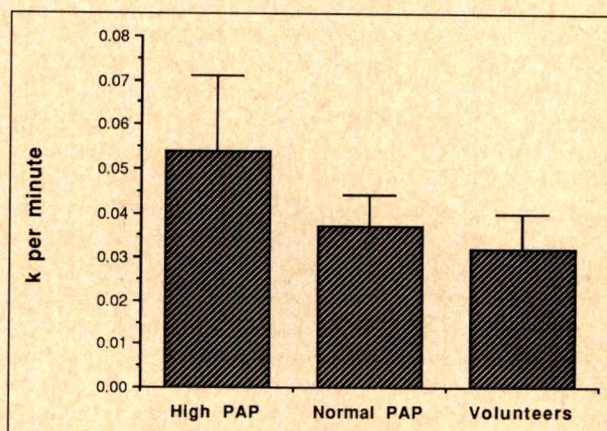


FIGURE 3. C-11 acetate clearance rate constants were, on average, significantly higher in 13 patients with elevated pulmonary artery pressure (PAP) than in 8 patients with normal pulmonary artery pressures and in 10 normal subjects (Volunteers). C-11 clearance was also slightly faster in patients with normal pulmonary artery pressures than in normal volunteers, possibly reflecting the fact that mean pulmonary artery pressures in this group of patients were in the upper end of the normal range.

constants and 5 potential predictors of RV oxygen demand including mean, systolic and diastolic pulmonary artery pressures, and RV rate-pressure product and heart rate (cumulative $r = 0.8$, $p = 0.006$). Similar comparison between C-11 acetate clearance rate constants in the septum and the same 5 parameters revealed no significant correlation (cumulative: $r = 0.6$, $p = 0.17$).

Comparison of each study subgroup showed that the ratio of RV free wall to septal C-11 acetate clearance rate constants was significantly higher in group II than in group I ($78 \pm 15\%$ vs $57 \pm 8\%$, $p < 0.005$) and in normal volunteers ($78 \pm 15\%$ vs $58 \pm 10\%$, $p < 0.005$). Also, although there was a significant difference in RV free wall C-11 acetate clearance rate constants in group II compared with group I (0.054 ± 0.017 vs 0.037 ± 0.007 , $p = 0.003$), there was no significant difference in C-11 clearance in the septum of the 2 subgroups (0.069 ± 0.014 vs 0.065 ± 0.011).

DISCUSSION

C-11 acetate has been validated as a tracer of myocardial oxidative metabolism in both animals^{16,19,20} and humans.²¹ We have previously shown the unique ability of C-11 acetate kinetics to provide noninvasive evaluation of regional LV oxidative metabolism.²² Based on these findings, we hypothesized that analysis of RV free wall C-11 acetate clearance kinetics should provide noninvasive evaluation of RV oxidative metabolism.

Our primary hypothesis could not be directly validated because of the inability to measure RV oxygen consumption directly. However, the positive correlation between RV free wall C-11 acetate clearance rate constants and RV hemodynamic data demonstrated in this study supports our hypothesis since increased loading conditions would be predicted to increase RV oxygen demand. Furthermore, lower C-11 acetate clearance rate constants were observed in the RV free wall than in the septum in both normal subjects and patients. This is consistent with the lower stroke work of the right ventricle compared with the left. There was a significant correlation between C-11 clearance rate constants in the RV free wall and septum ($r = 0.75$, $p = 0.0001$) supporting the functional interdependence of these regions.⁶ However, C-11 clearance rate constants correlated with pulmonary hemodynamics, whereas those in the septum did not. These data further suggest that regional RV clearance of C-11 acetate reflects local oxygen demand.

Pathophysiologic considerations: Myocardial oxygen consumption is determined by energy demand, which integrates the effects of myocyte loading, and the rate of isometric force production. Consequently, changes in cardiac performance that occur in pressure and volume overload of the right ventricle may alter the relation between loading conditions and oxygen demand.²³ In compensated RV hypertrophy resulting from pressure overload, performance of the right ventricle as assessed from pressure measurements may appear to be elevated but is essentially normal when corrected for volume²⁴ or RV mass.²⁵ However, depressed RV contractility would be expected to decrease oxygen consumption relative to a right ventricle with normal con-

tractile function under the same loading conditions. Assessment of RV loading alone, particularly in the failing ventricle, may give inadequate evaluation of myocardial oxidative metabolism. Under these conditions, C-11 acetate clearance kinetics that provide direct assessment of myocardial oxygen consumption, integrating both loading determinants of myocardial oxygen demand and the effects of altered contractility, may provide unique characterization of RV performance.

The scatter about the line of identity relating RV C-11 acetate clearance rate constants and RV rate-pressure products in our study group (Figure 2A) may well reflect the limitations of RV hemodynamics as predictors of RV free wall oxygen consumption rather than limitations of C-11 acetate kinetics in assessing regional oxidative metabolism. This was evidenced by the improved correlation between C-11 acetate clearance rate constants and the RV rate-pressure product when the 2 patients with RV failure were excluded from analysis (Figure 2B).

Study limitations: The major limitation of this study is the fact that RV hemodynamic data, with which C-11 acetate clearance rate constants were compared, were obtained at a different time than the PET study. Although these patients were clinically stable, had no change in medication in the study interval, and underwent both studies under similar conditions, the possibility that there might have been fluctuation in pulmonary artery pressures cannot be excluded. Standard right-sided cardiac catheterization was performed in all patients as part of routine clinical management. Consequently, more sophisticated evaluation of RV loading including pressure-volume loops²⁶ was not performed. These preliminary feasibility results in humans suggest that further assessment of the utility of PET with C-11 acetate is warranted in subgroups of patients with more advanced RV disease.

The RV free wall thickness is generally much less than the intrinsic resolution of the PET device used (8 to 10 mm). Nevertheless, correction for partial volume effects was not needed because C-11 acetate clearance rate constants are a rate of change in activity rather than an absolute measure of tissue activity and are thus insensitive to partial volume effects. A more important theoretical problem with these studies is the spillover of blood pool activity into the myocardial region of interest. Although C-11 acetate activity clears rapidly and substantially from the blood,¹⁴ the thin free wall of the right ventricle and the large adjacent blood pool make the effects of spillover relatively greater for the right ventricle than for the left ventricle.²⁷ Without accurate measurement of RV wall thickness and chamber diameters, correction of cross-contamination of recorded counts between blood and myocardium was not possible. However, the effects of spillover on C-11 clearance rate constants are likely to have been minor since fitting of the myocardial time activity was performed after the blood pool activity had largely cleared and was relatively stable.

Clinical implications: The unique ability of PET with C-11 acetate to provide noninvasive assessment of regional myocardial oxidative metabolism may provide

an attractive option for following patients with RV volume or pressure overload. Assessment of the success of medications in decreasing RV oxygen demand could be assessed, and the combination of noninvasive evaluation of RV size and performance obtained by echocardiography and PET with C-11 acetate could provide evaluation of the progression and status of RV dysfunction in various cardiac and pulmonary diseases. The findings of this study warrant application of this approach to diseases, such as primary pulmonary hypertension, scleroderma, and mitral valve disease, which are more frequently associated with RV dysfunction than is aortic valve disease.

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Validity of Catheter-Tip Doppler Technique in Assessment of Coronary Flow Velocity and Application of Spectrum Analysis Method

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Measurement of coronary flow velocity in clinical cases contributes to understanding the pathophysiology of coronary circulation. To determine absolute coronary flow velocity, coronary blood flow was assessed with an end-mounted Doppler catheter (3Fr, 20 MHz), which was combined with a custom-designed fast-Fourier transformation analysis system. In vitro study using model circuit, actual flow velocity (8 to 96 cm/s) was well correlated with that determined by this catheter system ($y = 1.01x + 1.5$, $r = 0.988$). In a clinical study of 12 patients with normal coronary arteriograms, the Doppler catheter was positioned at the proximal left anterior descending artery. Clear flow velocity patterns, which consisted of predominant diastolic components and preceding small systolic components, were obtained in all cases. The peak flow velocity was 17 ± 8 cm/s (mean \pm standard deviation) during systole and 44 ± 12 cm/s during diastole in this portion. In 5 patients, the great cardiac vein flow, which reflects the left anterior descending artery flow, was simultaneously measured during rapid atrial pacing. During pacing, percent increases in flow velocity were well correlated with those in great cardiac vein flow ($y = 0.90x + 6.4$, $r = 0.935$). These results indicate that catheter-tip Doppler technique with fast-Fourier transformation analysis may be useful in quantitatively determining coronary flow velocity in clinical cases.

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Recent advances in a catheter-tip Doppler technique have enabled us to estimate coronary flow velocity in clinical cases.^{1,2} With this method, functional capacity of coronary circulation such as coronary flow reserve has been determined to assess the severity of coronary stenosis.³ Although it is also intriguing to analyze the coronary flow velocity patterns with this technique, precise determination of flow velocity pattern has not been possible owing to methodologic limitations.⁴⁻⁶

Application of the fast-Fourier transformation spectral analysis method to analyze the signals from the Doppler catheter may enable us to estimate coronary flow velocity patterns. Johnson et al⁷ reported that in the experimental study absolute coronary flow velocity could be measured by a Doppler catheter system after spectral analysis. However, there has been no report in which the accuracy for determining flow velocity was systematically studied. In the present study, we attempted to examine the validity of a newly developed fast-Fourier transformation analysis system by which Doppler signals from a catheter-tip probe were analyzed in a model circuit and in clinical cases.

METHODS

Doppler catheter and signal analysis system: We used a commercially available 3Fr Doppler catheter with an end-mounted transducer (model DC-201, Millar Inc.) and a standard signal generator (model MDV-20, Millar Inc.). Precise information on these systems has already been described by others.^{2,7} Briefly, a carrier frequency was 20 MHz and a pulse repetition frequency was 62.5 kHz. The sample volume was 0.46 mm in depth, and movable from 1 to 10 mm from the catheter tip.

The quadrature phase detector had 2 outputs with a 90° phase difference between them, representing the instantaneous phase difference between the echo signal and the 20-MHz carrier frequency, and with the sign of the phase shift determined by direction of motion. Signals returning to the receiver were amplified and passed to a dual-face detector where 2 reference signals, locked to the transmitted frequency and separated in phase by 90°, were compared with the returning signal. Then, the audio signal was transmitted to a spectrum analyzer through a gain controller. After passing the analog to digital converter, digital signals that were periodically sampled from each channel were transferred to the pro-

cessor. In this system, it is possible to record not only the full power spectrum of flow velocity, but also the instantaneous mean flow velocity. Doppler signals after spectral analysis were recorded on a strip-chart recorder at a paper speed of 50 mm/s.

In vitro study: For the model circuit, we used polyethylene tubes with a 5-mm inner diameter and 40 cm in length. The tip of the Doppler catheter was placed at the midportion of this tube. The solution, which consisted of water, glycerin and sephadex particles ($\pm 4 \times 10^6/\text{mm}^3$), was injected with a direction away from the catheter tip by a Harvard pump at a rate of approximately 10 to 200 ml/s. The sample volume was set at 4 mm distal to the catheter tip to avoid the effect of flow turbulence.⁵ Measurement was performed 2 times at each flow rate. The relation between the mean flow velocity measured by the Doppler catheter and actual flow velocity, which was calculated by dividing the timed volume collections by cross-sectional area of the polyethylene tube (19.6 mm^2), was determined.

Human studies: We studied 12 patients (9 men and 3 women aged 53 to 68 years [mean 64]) with chest pain syndrome who had normal coronary arteries on angiography. Informed consent was obtained from all patients before catheterization. All antianginal drugs except oral nitroglycerin were discontinued 12 hours before the procedures. After diagnostic coronary angiography was performed using an 8Fr guiding catheter, heparin sodium (100 U/kg) was additionally given intravenously. The Doppler catheter was preloaded with a 0.014-inch flexible steerable guidewire. The guidewire was extended beyond the tip of the Doppler catheter and this system was passed through the guiding catheter into the proximal left anterior descending artery. Flow velocity patterns in the left main coronary artery were also determined in some cases. After dislocation of the guiding catheter from the wedged position, an optimal audio signal and a phasic tracing of maximal flow velocity were obtained by making minor adjustments in the position of the Doppler catheter.

In 5 patients who had exercise-related chest symptoms, rapid atrial pacing was performed to alter coronary blood flow. At this time, the great cardiac vein flow, which can be an index of the left anterior descending artery flow, was measured by the thermodilution method using an 8Fr multithermister catheter (CCS-8/7-90K, Wilton-Webster Corporation).⁸ The pacing rate was increased from 90 to 130 beats/min by 20 beats/min every 3 minutes, and coronary flow velocity and great cardiac vein flow were recorded just before the increment of the pacing rate. A standard 12-lead electrocardiogram was also recorded. In a clinical study, maximal flow velocity was determined by averaging the values of ≥ 5 consecutive beats.

Statistical analysis: Data were expressed as mean \pm standard deviation. The relation between 2 parameters was evaluated by a simple correlation analysis.

RESULTS

In vitro study: When flow rate was increased from 8 to 96 cm/s, mean flow velocity determined by the

Doppler method was well correlated with these values, giving a correlation efficient of 0.988. The regression line for these 2 variables closely approximated the line of identity, with a slope of 1.01 and y intercept of 1.5 (Figure 1).

Flow velocity of human coronary circulation: Flow velocity could be recorded in all patients examined. The flow velocity pattern in the proximal left anterior descending artery consisted of predominant diastolic components that were preceded by small systolic components. In 8 of 12 patients, there were transient and small reversal components at the phase of isovolemic contraction or atrial contraction, or both. As shown by the epicardial approach,⁶ flow velocity patterns in a representative case consisted of the relatively narrow band pattern (Figure 2). The peak flow velocity was $44 \pm 12 \text{ cm/s}$ during diastole and $17 \pm 8 \text{ cm/s}$ during systole.

The flow velocity pattern in the left main coronary artery was somewhat different from that in the left anterior descending artery. A representative pattern observed in 7 patients consisted of diastolic components that were preceded by systolic components with relatively high-flow velocity, probably due to the effect of aortic ejection (Figure 3).

Relation between coronary flow velocity and great cardiac vein flow: The pacing rate could be increased to 130 beats/min in 3 patients and 110 beats/min in 2 patients who had atrioventricular block at the rate of 130 beats/min. The electrocardiogram showed no significant ST-segment deviation in any patients. When the pacing rate was increased, great cardiac vein flow increased from 56 to 80 ml/min before pacing to 134 to 218 ml/min at the peak pacing rate. Under these conditions, peak flow velocity during diastole increased from 31 to 40 cm/s to 64 to 114 cm/s (Table I). When per-

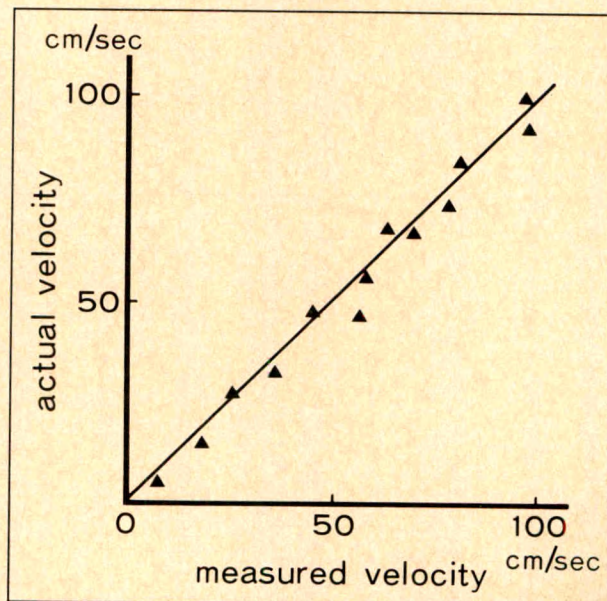


FIGURE 1. Relation between the actual flow velocity (*ordinate*) and measured mean flow velocity (*abscissa*) in the circuit model using a polyethylene tube with a 5-mm inner diameter. There is a good correlation between them ($r = 0.988$, $y = 1.01x + 1.5$).

TABLE I Summary of the Effect of Atrial Pacing on Coronary Flow Velocity and Great Cardiac Vein Flow

Pts.	Pacing Rate (beats/min)				Pacing Rate (beats/min)			
	Before	90	110	130	Before	90	110	130
	Flow Velocity (cm/s)				Great Cardiac Vein Flow (ml/min)			
1	31	74	88	114	56	138	156	196
2	32	70	80	112	60	124	144	198
3	34	85	106	110	66	171	190	218
4	33	72	80	—	72	166	172	—
5	40	42	64	—	80	88	134	—

cent increases in great cardiac vein flow and coronary flow velocity were compared at each pacing rate, a good correlation was found ($r = 0.935$, $y = 0.90x + 6.4$, Figure 4).

DISCUSSION

Improvements of Doppler catheter design have enabled us to estimate coronary flow dynamics¹⁻³ including the evaluation of the results of angioplasty.⁹ In these studies, analysis of the Doppler signal from the coronary circulation was made by a zero-crossing counter that produced a voltage proportional to the pulse fre-

quency. Although a zero-crossing analysis system is quite simple and convenient, this method is known to be inaccurate in areas of disturbed flow and incapable of detecting true peak velocities.⁴⁻⁷ Since the Doppler signal from coronary blood flow is the sum of bursts from the different scatterers, the full power-spectrum analysis such as fast-Fourier transformation analysis, which represents the average amount of power in the signal for each frequency, would be required to obtain all information in the composite Doppler signals from coronary blood flow.⁴⁻⁷

In the present study, the measured flow velocity in vitro model was well correlated with the actual flow velocity, and the measured flow velocities at the proximal left anterior descending artery were essentially similar to those measured by another method.¹⁰⁻¹³ This suggests that in clinical cases the present system can provide the accurate measurement of coronary flow velocity, although the great cardiac vein flow that we used as a reference of coronary flow has some limitations as a gold standard.¹⁴

As shown in a clinical measurement, complex spectral analysis has a major advantage. A flow velocity pattern consists of a narrow band that was not seen in the experimental measurement.⁷ Essentially, in the coronary artery, blood flow is laminar, representing the flow

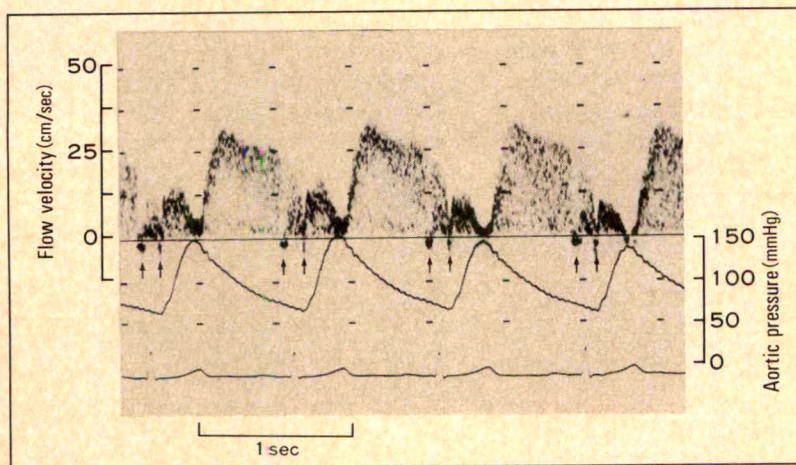


FIGURE 2. Representative flow velocity pattern at the proximal left anterior descending coronary artery. There were predominant diastolic components that were preceded by small systolic components. During isovolemic and atrial contractions, transient flow reversal was also observed (arrows).

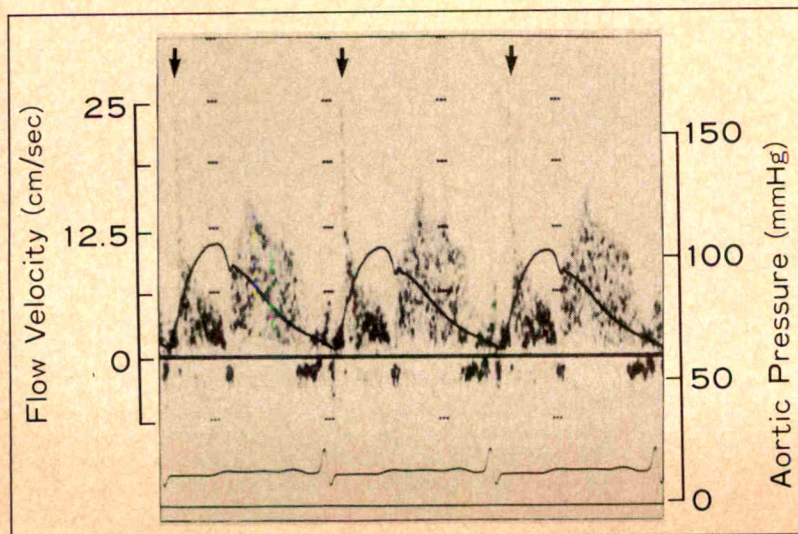
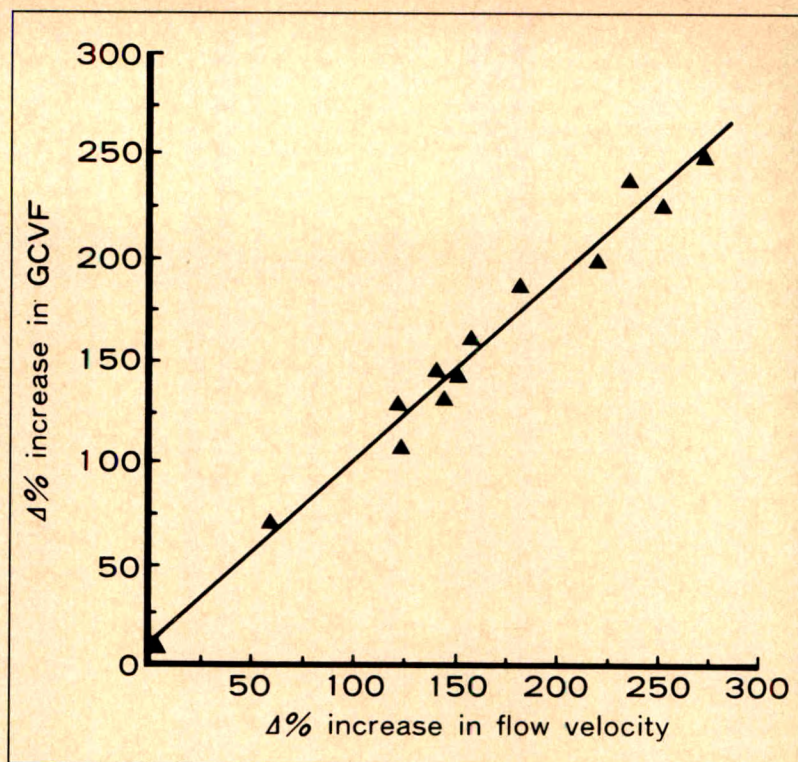


FIGURE 3. Representative flow velocity pattern at the left main coronary artery. There were systolic components (arrows) with patterns that were somewhat different from those observed in the left anterior descending artery. This may be due to the effect of aortic ejection during systole.

FIGURE 4. Relation between percent increases in great cardiac vein flow (GCVF) (ordinate) and those in the flow velocity of the proximal left anterior descending artery (abscissa) during rapid atrial pacing. There is a good correlation between them ($r = 0.935$, $y = 0.90x + 6.4$).



velocity pattern of a narrow band.⁶ Therefore, if a flow velocity pattern of a wide band is observed by the present method, this may indicate the presence of disturbed flow that resulted from artifacts such as the positioning of the catheter. This may be one of the advantages of the spectral analysis in distinguishing laminar from disturbed flow.

Clinical implications: Measurements of absolute coronary flow velocity may provide several clinical applications. Johnson et al⁷ estimated the severity of coronary stenosis by calculating the cross-sectional area using the formula of continuity equation. For this purpose, the present system may be applicable for measuring the absolute flow velocity at the site prior to stenosis and the site of stenosis of the human coronary artery.

Another clinical application of the present method is precise analysis of the flow velocity patterns. For example, the reverse of the flow direction in the coronary artery, which was already observed by the epicardial Doppler technique,⁶ was also demonstrated by the present system. It may be especially useful to examine the effect of a vasodilator drug such as nitroglycerin on these flow velocity patterns, including the reverse of the flow direction.

Study limitations: Important problems need to be resolved: First, the measurable maximal flow velocity, which is determined by the carrier and pulse repetition frequency, has still been approximately 115 cm/s, and aliasing occurs when coronary blood flow with higher velocity is measured. Thus, it is impossible to measure flow velocity through severe stenosis where coronary blood flow would be markedly augmented.¹⁵ In the future, technical advancements may allow use of high pulse-repetition frequency methods that would enable accurate measurement of high velocity flows character-

izing significant coronary stenosis. Second, the position of the Doppler catheter is still an important factor in obtaining the clear flow velocity patterns associated with maximal flow velocity. However, by carefully monitoring of the flow velocity pattern after spectral analysis, it is possible to adjust the catheter position at the optimal site where a narrow band pattern was observed.

Although we demonstrated that spectral analysis can provide precise information on Doppler signals from the coronary circulation, further studies are needed to examine whether zero-crossing or spectral analysis would be more suitable for analyzing the Doppler signals from a Doppler catheter.

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On Jumbo and Junk Trials: A Fumbled Affair, a Jungle, or the Ultimate Solution?

Paul G. Hugenholtz, MD

Let us not let the Genie escape from the bottle, again!" The author of that quote, Eugene Braunwald, used it in 1980 at the beginning of the new thrombolytic era.¹

Indeed, it seems as if the world has followed his advice because the recent series of thrombolytic trials that were conducted between 1980 and 1989—on both sides of the Atlantic Ocean and in Australia and New Zealand—have been an excellent example of how to conduct responsible clinical research. They provided early leads to the community of practicing cardiologists and general physicians on how to change the therapy of acute myocardial infarction fundamentally and how to avoid excesses by applying these therapies beyond where they are warranted. Compared with trial designs during the period between 1950 and 1980, when collectively more than 50,000 patients were subjected to investigations, most of which were not informative, the trial designs since the eighties have successively and successfully cleared the air.² Indeed, this time we seem to have handled the matter responsibly worldwide, and with a minimum of overlap, waste or excessive use of patient material. So why don't we stop here?

For example, do we really need a Third International Study of Infarct Survival (ISIS III) or a Global Utilization of Streptokinase and t-PA for Occluded Arteries (GUSTO) study, the current giants among the jumbo trials, to prove whether recombinant tissue-type plasminogen activator (rt-PA) or streptokinase (SK) is better? Is it really necessary to subject >30,000 people to uncertainty and another informed consent (and the agonies of that decision, let alone the explanations by the investigator) when we know the outcome to be limited in its information, if not irrelevant? For indeed those physicians who do not want to pay the higher price of rt-PA anyway (look at some national health care policies in Europe, the diagnostic-related groups philosophy in America or some hospital pharmacy directives) will stay with SK. Then there are those, of whom there are many, who argue that under a number of specific indications and circumstances (such as previous SK administration, large infarcts with much tissue at issue, imminent shock, late arrival but viable tissue, impending surgical interventions, out-of-hospital utilization,³ etc., etc.), they will prescribe rt-PA anyway and will circum-

vent all of these restrictions, for they want the "best" for their patients.

So the lesson we expect to be confirmed over the next 2 years, if the recent publication of the Second Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardio (GISSI)^{3,4} has not done this already, is that the profession will have made its mind up well before the answers of these jumbo trials *can* have come in. There is nothing against the scientific questions that are being asked in those studies, or against the notion that some jumbo trials *are* necessary. It is just that physicians (for better or worse) use other arguments than results from trials only. They *have* to act before all the facts are in or definitive battles between pharmaceutical houses are fought. Hence, should we not think of these giant trials like the junk bonds that are floating around on Wall Street these days in search of a new (unlikely) owner just as in a game of financial musical chairs? In short, do they really add to our fund of knowledge?

As argued earlier in this editorial, there *is* a need for large-scale trials if, as Yusuf et al⁴ state, "... the identification of effective treatment is likely to be more 'important' if the disease to be studied is common than if it is rare, and studies of common conditions can be large," and "... the identification of effective treatments for common diseases is likely to be more 'important' if the treatment is widely practicable than if it is so complex that it can be performed only in specialized centres, and treatment protocols for widely practical treatment can be simple..." and as "... the study of the effects of treatments on major endpoints (e.g. death) is likely to be more 'important' than study of the effects on minor endpoints, and follow up protocols for the assessment only on major endpoints *can* often be simple..." These statements, per se, are correct but do not constitute a "raison d'être," let alone a dominant and exclusive position in the clinical trial world.

Such large-scale trials, if they are to clarify the issue at hand, should be launched quickly and effectively if they are to be helpful. They lead us into the jungle, however, when they are used as Yusuf et al⁴ state: "No matter what prognostic features are recorded at entry, the duration of survival, etc., among apparently similar patients is likely still to be rather unpredictable, so no great increase in statistical sensitivity is likely to be conferred by stratification and/or adjustment for such features. In other words, the reliability of the main treatment comparison is improved surprisingly little by adjustment for any initial imbalances in prognostic features, which suggests that entry protocols too can be

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simple. . . .” For, even if these statements were to be true, large-scale trials cannot solve most outstanding clinical issues on an individual patient basis. Nor can their statement be correct “that trials *must* be large to provide reliable answers” or the conclusion that “a number of important medical questions will be answered reliably in the next few years *only* if some ultra-simple, ultra-large, strictly randomized trials can be mounted. . . .” We disagree, as these issues can sometimes better be resolved by other means, such as small, properly designed trials aimed at specific disease groups, disease stages or pathophysiologic questions (which can provide more specific and quicker answers⁵), backed up by nonexperimental efficacy research. We propose, in fact, a juxtaposition of these approaches, in which the Jumbo trial is reserved for specific public health issues only.

Nor is there much place for studies which, however exciting, do not provide sufficient statistical power to substantiate what might by itself be an exciting idea. A case in point is the recent article by Brown et al,⁶ which, on the basis of 146 patients divided into 3 treatment groups of 52, 46 and 48, respectively, comes to the conclusion that “in men with coronary artery disease who were at high risk for cardiovascular events, intensive lipid-lowering therapy reduced the frequency of progression of coronary lesions, increased the frequency of regression, and reduced the incidence of cardiovascular events.” The very placement of this article as a lead in the November 1990 *New England Journal of Medicine* suggests to the medical profession the opposite approach. This is that a limited number of observations can be so convincing that one is induced to conclude that all evidence is in already. For example, it would have been more appropriate, despite these careful and exciting observations, to state in the discussion section that confirmation of the clinical benefit of these observations was mandatory before clinicians could draw any conclusions as to the efficacy of this approach. This was not done; rather, the statement read that “clinical trials of treatment for coronary disease have typically enrolled several thousand patients for 5- to 10-year periods at costs that have often exceeded \$100 million. By contrast, this study, funded by the National Heart, Lung, and Blood Institute, cost less than \$1 million. Consequently, we believe that large-scale clinical trials should be reserved for interventions that have been shown convincingly, in smaller trials in which arteriography is used, to retard the progression of arterial obstruction or to promote its regression.”

Again, we would take the in-between position. Although we agree with Brown et al that “large-scale clinical trials should be reserved for interventions that have been shown convincingly, in smaller trials . . . ,” the evidence for such regression, or for that matter whatever intervention, should be substantiated considerably better before a recommendation for a large-scale trial can be made with pure clinical end points. After all, however exciting the initial trials for the possible regression or retardation of the development of atherosclerosis in the

coronary arteries may be, and however encouraging the progression of experimental evidence from animal models, it is the intermediate-scale trial in which the role of quantitative arteriography should be given its maximal opportunity. Although we agree with Brown et al that no clinical trial at great costs must be mounted until the underlying hypothesis is strong enough, we would side with Yusuf et al⁴ that “the identification of effective treatments for common diseases is likely to be more important, if the treatment is widely practicable, than if it is so complex that it can be performed only in specialised centres. . . .”

In short, a “trident,” 3-level approach appears, as it always has been, the best solution to a given clinical problem. It is this approach that the practicing cardiologist should insist on before changing his therapy: first, the original observation, anecdotal or observational in a limited series; then, the larger-scale, properly powered trial going for “surrogate” end points such as quantitative arteriography or ventricular function; and finally, ultimate substantiation by, if appropriate, the jumbo-sized trials advocated by Yusuf et al.

In closing, we plea for 2 decisions:

(1) Do not let another “Genie out again.” Let us recognize it: it takes 2 to tango, the clinician with his open “uncontrolled” observations, limited view but intrinsic knowledge of the patient, and the epidemiologist with his “blinded” analysis, nonbiased manner and adequate numbers (“power”) of the proper patient groups. Neither can replace the other. Both contribute to the truth, but only in part. They are complementary. In between lies the properly designed, numerically restricted trial to substantiate the underlying hypothesis.

(2) Do not let the “numbers game” take over our individual responsibility to diagnose each patient, patients whose ischemic situation will be changing from minute to minute. Ischemia is a cascade of events sometimes requiring quite different interventions in quick succession. Remember how the profession and the system together have brought mortality in myocardial infarction from >20% to <5% in just 10 years by first learning about the pathophysiology of the disorder. The essence of our cardiologic profession is at stake; we should not fumble.

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Effects of Superoxide Dismutase on Reperfusion Arrhythmias and Left Ventricular Function in Patients Undergoing Thrombolysis for Anterior Wall Acute Myocardial Infarction

Yoshiharu Murohara, MD, Yoshiki Yui, MD, Ryuichi Hattori, MD, and Chuichi Kawai, MD

Oxygen-derived free radicals have been implicated as important factors involved in the genesis of reperfusion injury. There is increasing evidence that a free radical scavenger, superoxide dismutase (SOD), limits reperfusion injury in animal experiments.^{1,2} We administered human recombinant SOD to patients with anterior wall acute myocardial infarction (AMI) at the time of thrombolysis and investigated (1) if SOD can reduce reperfusion arrhythmias, and (2) if SOD has beneficial effects on left ventricular function in the chronic phase.

We studied 34 consecutive patients with AMI treated by thrombolysis who fulfilled the inclusion criteria: no past history of myocardial infarction, chest pain of >20

minutes' but <6 hours' duration, electrocardiographic ST-segment elevation >1 mm in ≥2 contiguous anterior chest leads, age <75 years and angiographically proved occlusion of the proximal segment of the left anterior descending coronary artery even after intracoronary nitrate injection. Patients were excluded if they refused to participate or if they had previously had a stroke or had a confirmed peptic ulcer during the previous 6 months, systolic systemic blood pressure >200 mm Hg, or a history of a bleeding disorder. Patients with cardiogenic shock were also excluded.

After recognition of the obstruction in the infarct-related coronary artery, the patients were randomly allocated to SOD treatment or a control group. In SOD-treated patients, human recombinant SOD (Nippon Kayaku Co.) was given as a 3,500-U/kg bolus, followed by an infusion of 31,500 U/kg for the subsequent 2 hours. Immediately after beginning the SOD infusion, the procedure of coronary thrombolysis by tissue plasminogen activator or urokinase was begun. In the control group,

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TABLE I Patient Profile and Chronic Left Ventricular Function

	Sex/Age (yrs)	Time to Reperfusion (hr)	Regional Ejection Fraction (%)	
			Anterolateral	Apex
Control patients				
	F/68	4.0	0.9	1.3
	M/74	5.9	0.8	1.8
	M/35	2.6	44.1	33.2
	F/72	5.9	19.5	5.1
	M/41	2.3	56.7	38.5
	F/74	5.4	11.1	6.5
	M/69	5.8	4.5	17.3
	M/48	3.2	50.1	36.3
	F/37	2.8	39.5	40.2
	M/54	3.8	23.8	9.5
	F/50	4.9	1.1	2.6
	M/40	5.9	2.4	4.5
Mean	55.2	4.4	21.2	16.4
± SD	±14.7	±1.4	±20.3	±15.2
SOD patients				
	M/72	5.8	1.0	1.1
	F/71	4.9	20.8	33.5
	M/69	2.3	21.7	13.2
	F/57	2.0	58.8	39.8
	F/49	5.9	6.3	6.2
	M/50	2.2	57	35.1
	M/64	2.1	20.8	33.5
	M/58	5.9	11.8	18.5
	M/52	3.1	46.2	36.5
	M/46	4.8	0.5	2.2
	F/50	5.9	1.8	5.5
Mean	58.0	4.1	24.3	20.0
± SD	±9.1	±1.7	±21.6	±14.4

There were no significant differences between the 2 groups regarding age, time to reperfusion, and regional ejection fraction. SD = standard deviation; SOD = superoxide dismutase.

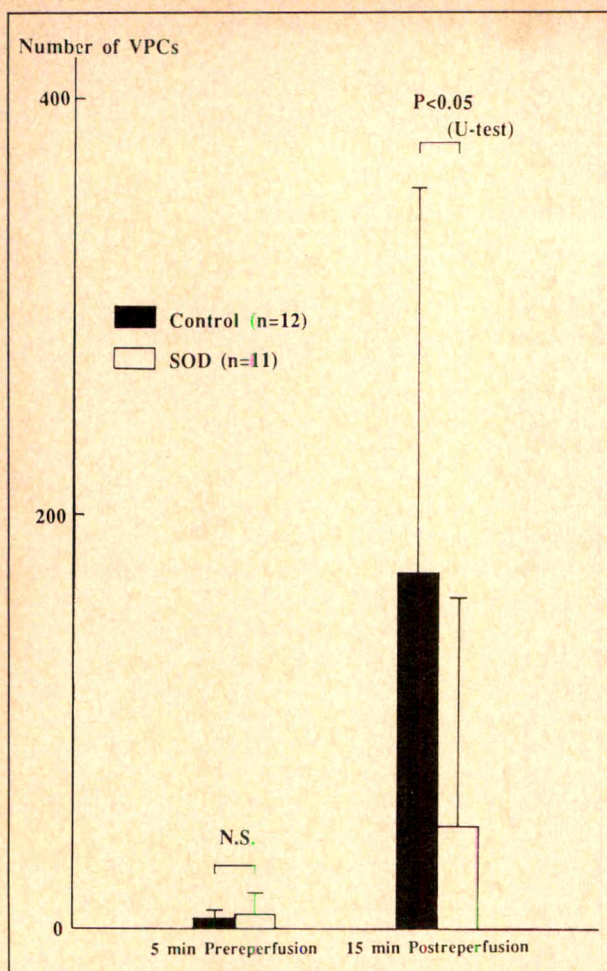


FIGURE 1. Total number of ventricular premature complexes (VPCs) during the period of 5 minutes before reperfusion (Prereperfusion) and 15 minutes after reperfusion (Postreperfusion). NS = difference not significant; SOD = superoxide dismutase.

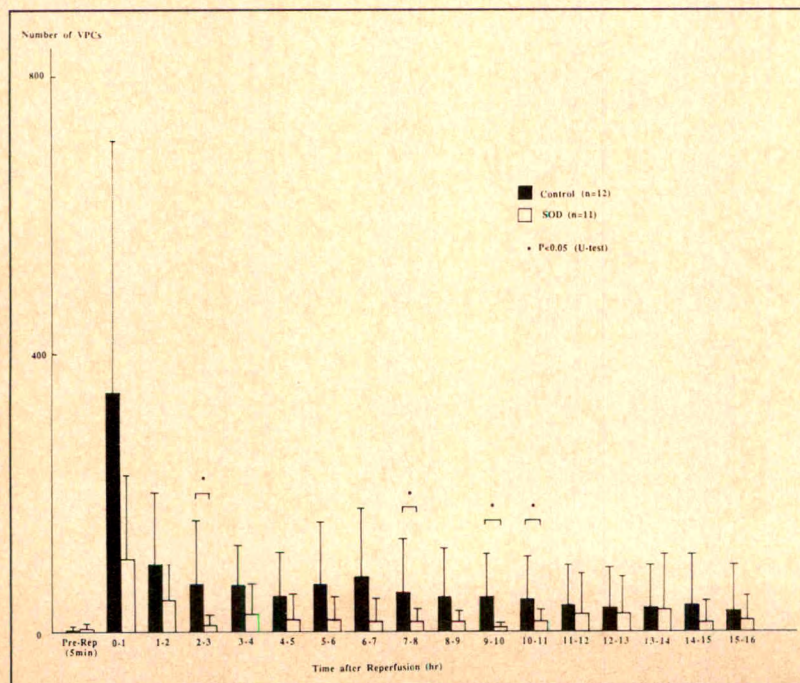


FIGURE 2. Total number of ventricular premature complexes (VPCs) per hour after coronary reperfusion. Pre-Rep = before reperfusion. SOD = superoxide dismutase.

thrombolysis was performed immediately after the study entry. As a rule, prophylactic use of antiarrhythmic drugs was prohibited before coronary reperfusion to analyze the effects of SOD on reperfusion arrhythmias. If necessary, 50 to 60 mg/hour of lidocaine was infused after thrombolysis (10 patients in the SOD group and 11 in the control group were treated with lidocaine infusion at doses of 52.0 ± 7.9 mg/hour and 55.5 ± 5.2 mg/hour, respectively).

Coronary recanalization was monitored by the abrupt occurrence of arrhythmias,³ the progressive resolution of ST-segment elevation or the abatement of chest pain, and was confirmed by subsequent angiography.

A 2-channel continuous Holter recording was begun immediately after study entry and continued until 16 hours after reperfusion. Ventricular premature complexes were counted manually on a complete recording printout, and we counted ventricular premature beats separately from those occurring during the runs of ventricular tachycardia. The term ventricular tachycardia was used when ≥ 6 consecutive ventricular premature contractions occurred.

Repeat cineangiography was performed 3 to 4 weeks after the onset of AMI. Regional ejection fractions were determined by the radial method⁴ from left ventriculography performed at the 30° right anterior oblique view.

Data are expressed as mean \pm standard deviation. The differences for patient profiles and left ventricular function were evaluated by the unpaired *t* test for comparison between groups. Comparison of the frequency of ventricular premature complexes was analyzed by the U test, with Wilcoxon's method. The occurrence of ventricular tachycardia was compared by the chi-square method.

Of the 34 consecutive patients with anterior AMI receiving thrombolytic agents, 25 (12, SOD; 13, control) had coronary recanalization of Thrombolysis in Myo-

cardial Infarction⁵ grade ≥ 2 . One patient in the control group had reocclusion of the infarct-related artery and 1 patient in the SOD group did not undergo repeat cineangiography because of cerebral infarction. The remaining 23 patients were analyzed.

Baseline characteristics of the SOD-treated and control groups were similar (Table I). No adverse reaction to SOD occurred.

During the first 15 minutes after coronary reperfusion, the incidence of ventricular tachycardia tended to be lower in the SOD group than in the control group (27 vs 58%, $p = 0.14$ by chi-square). The number of ventricular premature complexes during 15 minutes after reperfusion was significantly smaller in the SOD group than in the control group, although there was no difference in the counts of ventricular premature complexes during the 5 minutes before reperfusion (Figure 1). Ventricular fibrillation occurred in 1 control patient, and was converted to sinus rhythm with a defibrillator. The number of ventricular premature complexes per hour after reperfusion tended to be lower in the SOD group than in the control group. The difference was significant between 2 and 3, 7 and 8, 9 and 10 and 10 and 11 hours after reperfusion (Figure 2).

There was no difference in regional ejection fraction (anterolateral and apex) determined 3 to 4 weeks after the onset of AMI (Table I).

The present study supports the view of Nejima et al² that an intravenous administration of SOD had beneficial effects on reperfusion arrhythmias but not on left ventricular function. The reduction of arrhythmias by SOD also suggests an important role of superoxide anions in the genesis of reperfusion arrhythmias.

Failure to improve left ventricular function by treatment with SOD raises 2 possibilities. First, myocardial

cell injury during coronary reperfusion may be mediated not by superoxide anion but by other radical species, including hydrogen peroxide or hydroxyl radical.⁶ Second, it is possible that during the period before reperfusion, the infused SOD is not sufficiently delivered to the jeopardized myocardium because of a lack of adequate blood flow to that area. Our present study provides the basis for future randomized studies to establish the role of SOD as the therapeutic agent in patients undergoing thrombolysis. However, this is a pilot study to assess the hemodynamic effects and the overall feasibility of giving SOD in the human population. Further studies are needed to confirm the beneficial effects of SOD and to explore the possible adverse effects, if any.

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Incidence and Presumed Etiology of Ventricular Fibrillation During Coronary Angioplasty

Edmund Brennan, MD, Peter R. Mahrer, MD, and Vicken J. Aharonian, MD

Ventricular fibrillation (VF) is not an infrequent complication of percutaneous transluminal coronary angioplasty (PTCA).^{1,2} Similar to diagnostic coronary angiography, it is readily treated by defibrillation and death rarely results.³ There appears to be no relation to the severity of coronary artery disease, and the cause is probably partially related to the use of contrast agents.⁴ We analyzed in detail every case of VF occurring in 922 consecutive PTCA procedures.

The patient population comprised members of the Kaiser Permanente Health Plan in Southern California referred to the Regional Cardiac Catheterization Laboratory. For a PTCA to be considered, the following criteria were required: (1) angina that continued with adequate medical therapy, or ischemia demonstrated during exercise or thallium stress testing; and (2) diameter stenosis of >60% as measured by calipers in 2 orthogonal views. Single-vessel, multivessel and graft stenoses were treated. The patients' electrocardiograms were continually monitored. In patients with right coronary artery or dominant circumflex stenosis, a balloon-tipped pacemaker was advanced to the junction of the inferior vena cava and right atrium. The guiding catheter was used to perform angiography with 2 or 3 injections, which optimally demonstrated the lesion. Arterial pressure was continuously monitored from the tip of the guiding catheter, and if it differed from the previously recorded aortic pressure, the guide position was adjusted, or the guide was replaced by a different type, or one with side holes was used until an undamped pressure tracing was available. Immediately after the appropriate frames were selected, the balloon wire assembly was advanced through the guide and the wire manipulated across the lesion. Most of the time the guide remained in the vessel orifice during balloon and wire introduction. The duration of balloon inflation and the pressure was determined to attain an optimal angiographic appearance. Seventy-six percent of Hypaque® (diatrizoate sodium meglumine) was routinely used. Nonionic contrast was used only rarely in patients with ventricular impairment or ventricular irritability. VF occurred in 19 patients. The incidence of this arrhythmia was significantly higher ($p = 0.00017$) during PTCA of the right coronary artery ($n = 14$, 4%) than during PTCA of the left coronary artery ($n = 5$, 0.65%). In only 2 patients was the arrhythmia related to hemodynamic instability or prolonged ischemia. In most events VF took place before the balloon was inflated. There was no difference in severity of steno-

sis between left and right coronary arteries. Ejection fraction was satisfactory in most patients. One patient died in whom PTCA was attempted as a salvage procedure in the presence of cardiogenic shock where VF was a terminal rhythm. Another patient had vessel occlusion and subsequently myocardial infarction. In the remaining patients the procedure was completed without further ventricular arrhythmia.

VF is not an uncommon complication of coronary angioplasty. The incidence of VF was noted by Dorros et al¹ to be 1.6% in the report of the National Heart, Lung, and Blood Institute Registry series of 1,500 cases of coronary angioplasty. Bredlow et al² reported on the Emory experience in 3,500 patients in which 1.5% needed direct-current shock for ventricular arrhythmia. Ventricular arrhythmia occurred more often during PTCA of the right coronary artery. In Dorros' series, 33% of the patients with VF had a major complication (coronary artery bypass grafting, myocardial infarction or death), but in the Emory series only a small proportion required an intervention other than defibrillation. In our series, only 10% of the arrhythmias were due to occlusion of the vessel, whether by balloon or disruption, or to hemodynamic instability. Impaired left ventricular function was confined to that same group because in most patients the ejection fraction was normal. Thus, the usual cause of VF, as seen during acute coronary artery occlusion, plays only a minor part in the development of VF during angioplasty. In seeking the mechanism of VF in most patients, one must examine the incidence of this arrhythmia during diagnostic angiography.⁵ Several large retrospective series have examined the incidence of VF during diagnostic studies. Nishimura et al⁴ reported a 0.5% incidence, 62% of which occurred during right coronary artery injections. They concluded that although VF can be caused by ischemia or mechanical complications, almost all VFs have been associated with contrast toxicity. Davis et al⁶ reported an incidence of 0.6%, and Johnson et al⁷ reported an incidence of 0.56% of significant arrhythmia during coronary arteriography. Contrast material decreases the threshold for VF.^{8,9} Ischemia, slow prolonged injection, and injection through impacted catheters was noted to lower VF threshold disproportionately. The use of non-ionic contrast agents, agents with supplemental calcium added, and agents without calcium ion-sequestering stabilizing agents have been associated with a decreased risk of VF during coronary angiography.¹⁰⁻¹⁴ Murdock et al¹⁵ demonstrated in canine experiments that repolarization changes reliably preceded the occurrence of VF, changes that were all but eliminated by modification of the contrast agent. The role of contrast agents in the genesis of VF is thus well established; however, 2 questions remain to be answered. First, why is the incidence of VF higher

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during PTCA than during diagnostic angiography, even when the obvious causes of vessel obstruction or ventricular dysfunction are removed? Second, why is there a marked discrepancy in the incidence of right and left coronary artery injections?

Occlusion by the guide or contrast injection into the sinus node artery plays only a small part—in our series only one case was associated with significant bradycardia. Answers to both questions are likely related to impairment of flow and stagnation of contrast in the vascular bed. The guiding catheters are larger than the standard 7Fr size used in diagnostic studies. Although we meticulously monitored pressures, this does not assure that adequate flow was present, particularly in cases in which side holes in the guide were necessary to attain a good pressure contour. Damping of pressures and the need for side holes is much less frequent during cannulation of the left main coronary artery. We believe that stagnation of contrast material in the vascular bed supplied by the right coronary artery is the major and largely avoidable cause of VF during angioplasty.

The preventive procedures in avoiding this troublesome complication are obvious, and we are currently gathering data to confirm the efficacy of reducing the rate of VF by removing the right guiding catheters from the orifice during wire and balloon introduction, by flushing the orifice with saline solution if the ostium is difficult to cannulate, or by using nonionic contrast during PTCA of the right coronary artery.

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Comparison Between Ventricular Inhibited Pacing and Physiologic Pacing in Sick Sinus Syndrome

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Sick sinus syndrome (SSS) causes not only infrequent cardiac dysfunction but also systemic complication, and pacemaker implantation has been applied to prevent such an episode. Several kinds of pacemakers have been available for clinical use. However, the selection of these pacemakers has been controversial depending on the severity and character of the conduction system impairment accompanying SSS. We have already reported the long-term follow-up results in patients with SSS who had not had a pacemaker or had implanted pacemakers of various modes.¹ In that report, we found that the ventricular inhibited paced (VVI) group had significantly more complications and a greater cardiothoracic ratio after pacing in the follow-up period than the physiologically paced groups. We concluded that the decision to use VVI pacing needed to be carefully assessed in patients with SSS, and that physiologic pacing is more highly recommended. However, the study population in that report was small and the follow-up period was short. In this article, we report the results of our further study with a larger population and longer follow-up.

This time we selected and confined our study to the patients with SSS who received a permanent pacemaker. The physiologic groups consisted of 23 men and 18 women (mean age 63 years, range 29 to 81); the VVI group

consisted of 15 men and 19 women (mean age 69 years, range 38 to 85). Patients in the VVI group were significantly older than those in the physiologic group ($p < 0.05$). When both groups were classified according to Rubenstein's criteria, the incidence especially of Rubenstein's type III arrhythmia was almost similar in both groups. The follow-up periods in the VVI group were significantly longer (39 months) than those in the physiologic group (62 months) ($p < 0.01$). No statistically significant difference was noted in the underlying diseases of SSS between the physiologic and VVI groups (Table I). In both groups, the cardiothoracic ratio decreased significantly shortly after implantation (discharge) (Figure 1). However, in the long follow-up period, the cardiothoracic ratio of the VVI group increased significantly ($p < 0.05$) and was greater than the ratio before operation. In fact, the cardiothoracic ratio tended not to increase in the physiologic group, and remained decreased (Figure 2). In both the VVI and physiologic groups, the pacemaker was operated all or at least most of the time, i.e., pacemaker-dependent. The atrial inhibited paced (AAI) mode was implanted in 17 of 41 patients (41%) in the physiologic group. The maximal atrioventricular interval in dual chamber pacing (DDD) was chosen in each generator used. In all, a pacemaker system of atrial paced and ventricular sensed modes was operated in 28 patients. Because a pacing spike-QRS interval is considered one of the parameters of atrioven-

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TABLE I Underlying Diseases

	Physiologic Group (n = 41)	VVI Group (n = 34)
Systemic hypertension (%)	10 (24)	10 (29)
Coronary artery disease (%)	2 (5)	5 (15)
Valvular heart disease (%)	2 (5)	2 (6)
Diphtheria (%)	5 (12)	0 (0)
Myocardial disease (%)	1 (2)	0 (0)
Amyloidosis (%)	1 (2)	2 (6)
Diabetes mellitus (%)	2 (5)	4 (12)
Thyroid disease (%)	1 (2)	0 (0)
Familial (%)	0 (0)	1 (3)
Persistent left superior vena cava (%)	1 (2)	0 (0)
Progressive systemic sclerosis (%)	1 (2)	0 (0)
Ebstein's disease (%)	1 (2)	0 (0)
Wolff-Parkinson-White syndrome (%)	0 (0)	1 (3)
Unknown (%)	16 (39)	14 (41)

VVI = ventricular inhibited paced.

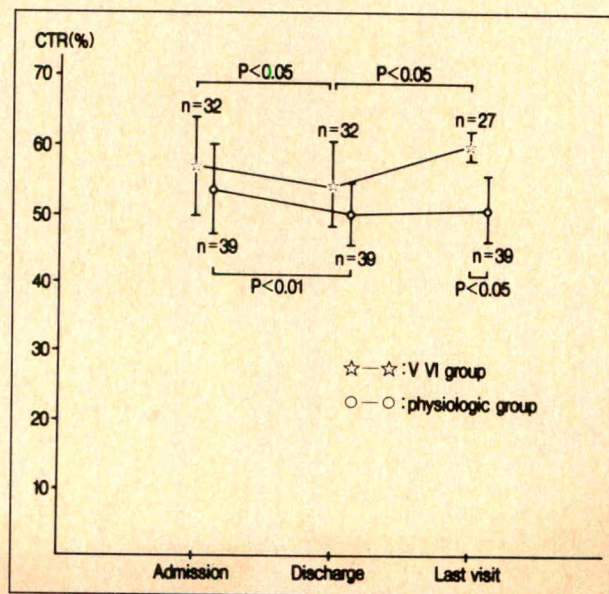


FIGURE 1. Temporal changes in cardiothoracic ratio (CTR) in physiologic and VVI pacing groups.

TABLE II Complications and Clinical Outcome After Pacing in Both Groups

	Physiologic Group (n = 41)	VVI group (n = 34)	p Value
Atrial fibrillation	7	15	<0.05
Paroxysmal	6	1	NS
Chronic	1	14	<0.01
Thromboembolism	1	9	<0.01
Congestive heart failure	1	7	NS
Cardiac death	0	8	<0.01
Congestive heart failure	0	3	NS
Thromboembolism	0	5	<0.05

NS = not significant; other abbreviations as in Table I.

tricular conduction, these 28 patients were examined annually for this interval (Figure 2). Significant increase of spike-QRS interval was not found over a follow-up period of 6 years. However, there were new developments in first and second atrioventricular block in 2 patients receiving the AAI mode 1 and 2 years after implantation, respectively. The atrioventricular block in these 2 patients was transient and they did not need to have the pacing mode changed. The VVI group had atrial fibrillation more frequently than the physiologic group (44 vs 17%, $p < 0.05$), especially chronic in character (41 vs 2%, $p < 0.01$) (Table II). Thromboembolism occurred more frequently in the VVI group than in the physiologic group (26 vs 2%, $p < 0.01$); however, the incidence of heart failure was similar in both groups. Five deaths in the physiologic and 12 in the VVI group occurred during the follow-up period. No death was from cardiac causes in the physiologic group; 8 deaths in the VVI group were of cardiac origin. This difference was statistically significant ($p < 0.01$). The causes of cardiac death were congestive heart failure and fatal thromboembolism, probably caused by atrial fibrillation. Thromboembolism oc-

curred significantly more frequently in the VVI group than in the physiologic group ($p < 0.05$). Figure 3 (overall survival rate) shows that the physiologic group had excellent prognosis, with a survival rate >4.8 to 7 years, which was statistically better than that in the VVI group ($p < 0.05$). When the causes of death were confined exclusively to cardiac origin, the survival rate was much more excellent in the physiologic than in VVI group for 3.2 to 7 years of follow-up, with statistical significance at $p < 0.01$ (Figure 4).

Considering the natural history of unpaced SSS, the development of atrioventricular block and atrial tachyarrhythmia, especially of atrial fibrillation during the clinical course, has been well known. With regard to permanent pacing for patients with SSS, the pacing modes should be selected based on what influence the pacing mode has on the incidence of atrioventricular block, atrial tachyarrhythmia, systemic thromboembolism, congestive heart failure, and eventually on the mortality rate after long-term follow-up. In a recent detailed review of published reports, Sutton and Kenny² reported that the prevalence of second-degree or greater atrioventricular block in patients with SSS who received AAI pacemakers was 8% (mean follow-up time 34 months). Kallryd et al³ also described a 6% incidence for a mean follow-up of 26 months. In our study, the incidence of atrioventricular block was 11% (2 of 17) in patients with AAI pacing. However, when we analyzed the 28 patients whose pacing mode was atrial-paced and ventricular-sensed including those with DDD pacing, it was 7% (2 of 28). There were no atrioventricular conduction abnormalities in these 2 patients as assessed by the PQ interval, Wenckebach rate <120 beats/min, prolongation of AH and HV intervals, and bundle branch block evaluated by preimplantation Holter recording and electrophysiologic study. If detailed preimplantation examinations including electrophysiologic study could be performed, we might not need to

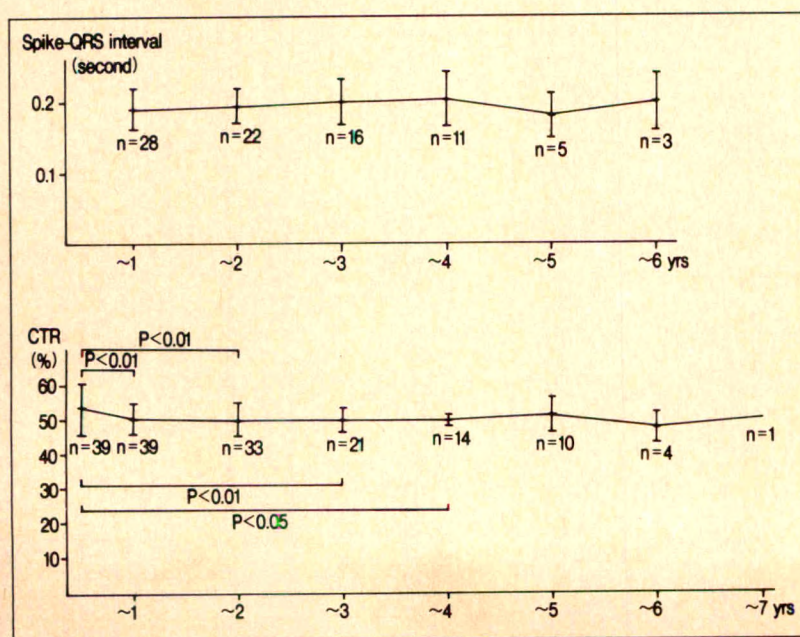


FIGURE 2. Serial changes in spike-QRS intervals and cardiothoracic ratio in physiologic pacing groups.

worry about the impending atrioventricular block during the follow-up time, even with use of AAI pacing. However, we have not had parameters sufficient enough to presume impending atrioventricular block. There is no exact way to know who will develop future atrioventricular blocks, except to do careful follow-up of patients receiving the AAI pacemaker. Because atrial fibrillation occurring in the follow-up period can lead to complications such as systemic thromboembolism, enlargement of cardiothoracic ratio and even congestive heart failure, its clinical development must be prevented. Sutton and Kenny² reported that the incidence of atrial fibrillation occurring in patients receiving AAI pacing was 3.9% (16 of 410) (mean follow-up time 32.8 months), significantly less (22% [145 of 651]) than the incidence in VVI-paced patients. Markewitz et al⁴ also reported the high inci-

dence of atrial fibrillation in the VVI-paced group after 5 years of follow-up (55 vs 11%). Our data are in line with theirs. Chronic atrial fibrillation occurred in 41% of patients receiving VVI pacing and in only 2% of those with physiologic pacemakers. Because the administration of antiarrhythmic drugs could not prevent this higher incidence of atrial fibrillation in the VVI-treated group, the choice of the VVI pacing mode should be carefully made. Sutton further reported that the incidence of thromboembolism was 1.6% (5 of 321) in patients receiving AAI, which was significantly less (13% [69 of 532]) than that in the VVI patients ($p < 0.001$). In contrast, Rosenqvist et al⁵ did not find any significant difference in the frequency of this complication between pacing modes. In our series, the VVI group had significantly more thromboembolism than did the physiologic group (26 vs 2%, $p < 0.01$).

FIGURE 3. Overall survival rate in physiologic and VVI pacing groups. Survival rate was better in the physiologic than in VVI group in follow-up period of 4.8 to 7 years.

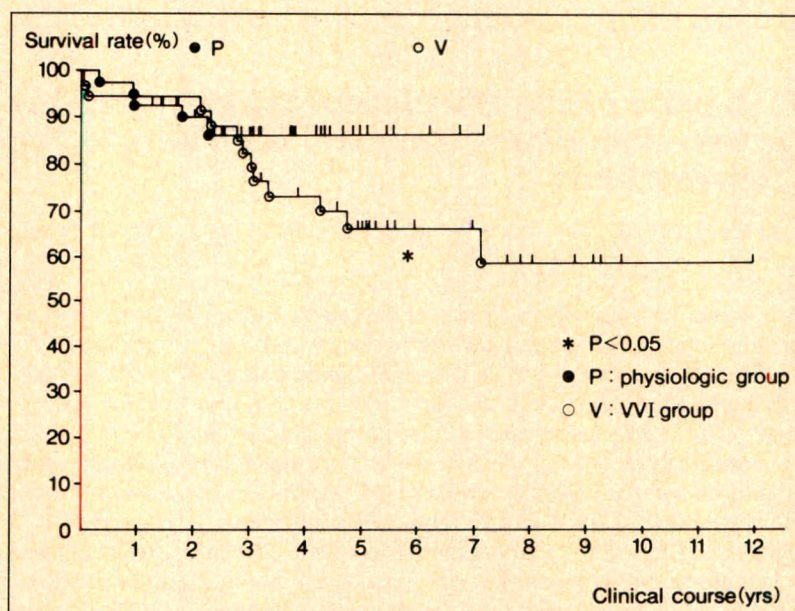
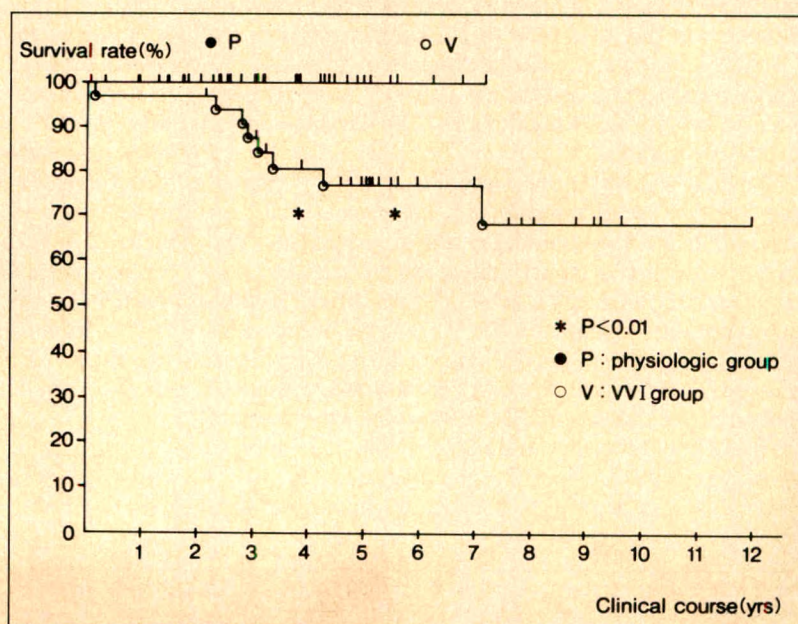


FIGURE 4. Survival rate of cardiac deaths in physiologic and VVI pacing groups. Excellent prognosis in the physiologic group was demonstrated.



There are a few comparative long-term follow-up reports dealing with survival rate after pacing. Alpert et al⁶ described that patients with SSS who had had congestive heart failure and an implanted DDD pacemaker had significantly excellent prognosis. Rosenqvist⁵ reported a higher overall mortality rate in the VVI than in the AAI group (23 vs 8%, $p < 0.05$). Sutton and Kenny² pointed out, in reviewing published reports, that it would still be too early to assess the possible benefit in the physiologic pacing system, and added that VVI pacing probably would not reduce mortality. In our study, the physiologic pacing groups had an excellent survival rate compared with the VVI pacing group. To answer the question asked by Sutton, a much more comparative long-term study between physiologic and VVI pacing in a larger population is needed.

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Variability of the QT Measurement in Healthy Men, with Implications for Selection of an Abnormal QT Value to Predict Drug Toxicity and Proarrhythmia

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Torsades de pointes is the form of polymorphic ventricular tachycardia associated with prolongation of the QT interval that can occur as a proarrhythmic adverse response to a variety of drug treatments.^{1,2} However, the degree of QT prolongation at rest^{3,4} or during exercise⁵ is not necessarily a good predictor of the occurrence of torsades de pointes. Prolongation of the QT interval duration is seen during therapy with many different types of drugs including class IA antiarrhythmic agents as well as ketanserin, amiodarone, bepridil, sotalol, antidepressants, phenothiazines, erythromycin, antihistamines and liquid protein diets. Quinidine is the drug most frequently implicated in this syndrome with a calculated incidence of 1 to 8%.⁴ However, plasma drug level, absolute QT interval prolongation and the absolute QT_c have not been found to be very good predictors of the development of torsades de pointes.^{3,4}

Data on the spontaneous variability of the QT interval over time in normal subjects have not been established. Thus, we determined the magnitude of spontaneous QT interval variability over just 1 day using ambulatory long-term electrocardiographic (Holter) monitoring. Knowledge of normal variability of the QT interval is important in that prolongation of the QT interval during drug therapy is considered to be a risk factor for the development of a potential proarrhythmic effect. However, knowledge of the daily spontaneous variability of the QT interval makes it possible to determine the magnitude of QT interval prolongation, which is clinically important with

respect to its potential as a marker for risk of proarrhythmia.

Twenty healthy men (mean age \pm standard deviation 40 ± 8 years [range 25 to 53]) were studied. All subjects had a normal history, physical examination, resting electrocardiogram, normal exercise treadmill test and normal echocardiogram. No subjects were taking drug therapy. We chose this group of volunteers to be more similar in age to patients seen in the usual adult cardiology practice who might be treated with drugs.

Subjects were studied in an inpatient unit to ensure a controlled stable state. The patients underwent 24 hours of Holter monitoring with an Avionics recorder (Delmar Avionics Corp., Irvine, California) with a reel-to-reel recorder that monitored leads V₁ and V₅. The QT interval of lead V₅ was measured 3 times per hour when the heart rate was <100 beats/min by a digitization procedure (Jandel's Sigma Scan software, Sunnyvale, California). This yielded 870 separate QT interval measurements. The QT_c was subsequently computed using Bazett's formula.⁶ Clinical judgment was used to define the junction between the T and U waves.

Statistical analysis was performed using a t test with significance at $p < 0.05$. All values given in the text are mean \pm standard deviation.

TABLE I QT_c Variability Over 24 Hours of Holter Monitoring

Time Segment	Range of RR Intervals (ms)	Average QT _c (ms)	SD (ms)	No. of Intervals
8 a.m.-4 p.m.	552-1,284	401	34	264
4 p.m.-12 a.m.	597-1,328	407	35	324
12 a.m.-8 a.m.	670-1,451	403	11	282

SD = standard deviation.

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In this group of normal men, the QT_c averaged 404 ± 34 ms ($n = 870$; $QT = 368 \pm 41$ ms, $RR = 840 \pm 161$ ms). When the day was divided into three 8-hour segments, the average calculated QT_c varied by 6 ms (Table I). The average pooled QT_c was relatively constant over the day and was not greatly influenced by circadian rhythm.

For individual subjects, the QT_c showed a large degree of daily variability ($p < 0.05$); the QT_c varied over the 24 hours of Holter monitoring by an average of 76 ± 19 ms (range 35 to 108 ms, Table II). This large magnitude of QT_c variability was present during each of the three 8-hour segments of the 24-hour Holter monitoring period, indicating that the QT_c varied by a large magnitude not only over the entire day, but also throughout each of the 8-hour segments of the day. In individual subjects, the QT_c changed from normal (<440 ms) to abnormal (≥ 440 ms) in 11 of the 20 subjects (55%), and exceeded 500 ms in 1 of the 20 subjects (5%) (Table II).

The subjects were then subdivided into groups. First, subjects with QT_c s that varied by <76 ms were compared with subjects whose QT_c s varied by ≥ 76 ms. Five (56%) of the 9 subjects with QT_c variability less than the average (76 ms) had ≥ 1 QT_c abnormal value (≥ 440 ms), compared with 6 of the 11 patients (55%) with greater than average QT_c variability (difference not significant). Next, the subjects ($n = 9$) whose QT_c values varied only within the normal range (<440 ms) were compared with those who had ≥ 1 abnormal QT_c value ($n = 11$). The QT_c varied by 73.4 ± 18.3 ms in patients in whom all measured values of the QT_c were normal compared with those with ≥ 1 abnormal QT_c in which the QT_c varied by 77.3 ± 20.8 ms (difference not significant). Thus, prolongation of the QT_c to abnormal values (≥ 440 ms) and the absolute magnitude of the variability in the QT_c were independent of one another in these normal men.

This study using ambulatory Holter monitoring as a surrogate of the supine resting electrocardiogram demonstrates that in normal men the QT_c has a high degree of spontaneous variability even over a single day under stable conditions, and the magnitude of that variability was 76 ± 19 ms. In these normal subjects, 55% had QT_c values >440 ms and 5% had QT_c values >500 ms over a 24-hour period.

The normal QT_c is often stated to be <440 ms.^{7,8} However, strong evidence that the upper limit of normal QT_c is 440 ms does not exist. Originally this range was supported by only 3 references, 2 of which were studies in children.⁷ Reviewing a 1,300 electrocardiographic data base of healthy subjects, it was found that the normal QT_c ranged from 463 to 506 ms,⁹ which is similar to the range of QT intervals (336 to 487 ms) reported in 50 normal subjects by Mirvis.¹⁰ In agreement with our results, these studies demonstrate that the normal QT_c is highly variable.

Several studies have found that the development of the torsades de pointes form of ventricular tachycardia is most frequently seen after a postectopic or post-tachycardic compensatory pause¹ and some investigators⁴ have suggested that a risk of a torsades de pointes increases greatly when the QT interval increases >500 to 550 ms.

TABLE II QT_c Variability for Individual Subjects

Subject No.	Age (yr)	QT_c Variability* (ms)	$QT_c > 440$ msec† (%)
1	49	91	49
2	50	93	8
3	34	86	0
4	40	66	17
5	36	61	6
6	49	76	61
7	29	56	0
8†	53	84	74
9	43	63	16
10	40	74	3
11	44	35	24
12	39	77	0
13	43	62	0
14	37	108	3
15	33	100	2
16	28	86	0
17	43	102	0
18	40	82	0
19	25	42	0
20	49	68	0
Mean	40 ± 8	76 ± 19	13 ± 22

* Defined as longest QT_c —shortest QT_c measured in each subject.

† Defined as the number of abnormal QT_c values/total number of measured QT_c values measured in each subject.

‡ Subject no. 8 had 3 QT_c values >500 ms.

Kay et al¹¹ reported on 32 patients who developed torsades de pointes as a result of antiarrhythmic therapy; before initiating therapy, 88% of these patients had a $QT_c > 440$ ms and 9% had a $QT_c > 500$ ms on baseline electrocardiogram. These findings are similar to results from our study of normal persons. We may expect that at baseline, QT_c values would exceed 500 ms in 5% of the patients and the QT_c values would be ≥ 440 ms in 55% of patients. Kay et al¹¹ reported that, after quinidine therapy, the QT_c was abnormal (≥ 440 ms) in 100% of the patients, the QT_c exceeded 500 ms in 84% of the patients and the average QT_c increased by 131 ms (from 463 ± 59 to 594 ± 84 ms). This is in general agreement with the results reported by others^{1,12} and consistent with our recommendations. Namely, we suggest that for a clinically important marker of a proarrhythmic drug effect that could lead to polymorphic ventricular tachycardia, syncope or sudden death rather than just a $QT_c > 440$ ms, a clinically significant change in the QT_c occurs when $>5\%$ of treated subjects have QT_c values >500 ms or when an individual patient has a change in the QT_c of >75 ms.

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Prevalence and Severity of Valvular Aortic Stenosis Determined by Doppler Echocardiography and Its Association with Echocardiographic and Electrocardiographic Left Ventricular Hypertrophy and Physical Signs of Aortic Stenosis in Elderly Patients

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Calcific deposits in the aortic valve are common in elderly persons and may lead to valvular aortic stenosis (AS).^{1–3} We performed a prospective study to determine the prevalence and severity of valvular AS by Doppler echocardiography and its association with echocardiographic and electrocardiographic left ventricular (LV) hypertrophy and with physical signs of AS in unselected elderly patients in a long-term health care facility.

M-mode and 2-dimensional echocardiograms and continuous-wave Doppler recordings for determining the prevalence and severity of AS were obtained as previously described.⁴ M-mode and 2-dimensional echocardiograms for measuring LV transverse dimension, posterior wall thickness, and interventricular septal thickness at end diastole using the Penn convention⁵ to determine LV mass were obtained as previously described.⁶ Electrocardiograms to determine the presence of LV hypertrophy were also obtained. Technically adequate recordings for determining the prevalence and severity of AS and its association with echocardiographic LV hypertrophy were obtained in 781 of 964 patients (81%).

The 781 patients included 558 women and 223 men (mean age \pm standard deviation 82 ± 8 years, range 62 to 100). All patients underwent a cardiovascular examination performed by a cardiologist before interpretation of the echocardiograms and Doppler recordings. A systolic ejection murmur heard in the second right intercostal space, down the left sternal border toward or at the apex was classified as aortic systolic ejection murmur.

The peak transvalvular gradient was determined by using the simplified Bernoulli equation: $\Delta P = 4V^2$, where ΔP = peak pressure gradient and V = peak transvalvular flow velocity. Peak flow velocity across the aortic valve ≤ 1.5 m/s was defined as normal (no gradient). Peak aortic flow velocity 1.6 to 2.5 m/s (peak gradient 10 to 25 mm Hg) was defined as mild AS. Peak aortic flow velocity 2.6 to 3.5 m/s (peak gradient 26 to 49 mm Hg) was defined as moderate AS. Peak aortic flow

velocity ≥ 3.6 m/s (peak gradient ≥ 50 mm Hg) was defined as severe AS.

The formula^{5,7} to determine LV mass was LV mass (g) = $1.04 [(LV \text{ diastolic dimension} + \text{posterior wall thickness} + \text{interventricular wall thickness during diastole})^3 - (LV \text{ diastolic dimension})^3] - 13.6$. LV hypertrophy was diagnosed if the LV mass exceeded 110 g/m² in women and 134 g/m² in men.⁷ All echocardiograms and Doppler echocardiograms were interpreted by an echocardiographer (I.K.).

Electrocardiograms were interpreted by a cardiologist before interpretation of the echocardiograms. Electrocardiographic LV hypertrophy was diagnosed if the point score of Romhilt and Estes was ≥ 5 .⁸ Chi-square analysis was used to analyze data.

Congestive heart failure, syncope or angina pectoris was present in 18 of 74 patients (24%) with mild AS, in 30 of 49 patients (61%) with moderate AS, and in 17 of 19 patients (89%) with severe AS. Table I lists the prevalence of echocardiographic and electrocardiographic LV hypertrophy in patients with mild, moderate and severe AS, and levels of statistical significance.

An aortic systolic ejection murmur was heard in 19 of 19 patients (100%) with severe AS, in 49 of 49 patients (100%) with moderate AS and in 70 of 74 patients (95%) with mild AS. The intensity of the aortic systolic ejection murmur, maximal location of the aortic systolic ejection murmur, transmission of the aortic systolic ejection murmur to the right carotid artery, and presence of an aortic ejection click did not differentiate between

TABLE I Prevalence of Echocardiographic and Electrocardiographic Left Ventricular Hypertrophy in Patients with Mild, Moderate and Severe Valvular Aortic Stenosis

Severity of AS	No. of Pts.	Left Ventricular Hypertrophy	
		By Echo.	By Electro.
		No. of Pts. (%)	No. of Pts. (%)
Mild AS	74	55 (74)*	8 (11)
Moderate AS	49	47 (96)*	15 (31)
Severe AS	19	19 (100)†	11 (58)

* $p < 0.001$; † $p < 0.005$.

AS = aortic stenosis; Echo. = echocardiography; Electro. = electrocardiography.

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mild, moderate and severe AS. Table II lists the prevalence of other physical signs of AS and levels of statistical significance in patients with mild, moderate and severe AS. No physical sign of AS differentiated between severe and moderate AS.

Continuous-wave Doppler recordings correlate well with direct pressure gradient measurements derived from cardiac catheterization in patients with AS.⁹⁻¹² Aortic valve area can be calculated by the continuity equation using pulsed Doppler echocardiography to evaluate LV outflow tract velocity, continuous-wave Doppler echocardiography to evaluate transvalvular flow velocity, and 2-dimensional long-axis view to measure LV outflow tract area.¹² This method was not always feasible in our elderly population. However, peak aortic flow velocities ≥ 3.6 m/s are almost always associated with severe AS, whereas low peak aortic flow velocities are almost always indicative of mild AS.¹¹ However, in some patients, severe AS may lead to a significant reduction of cardiac output and decrease in transvalvular gradient, or high transvalvular flow may create a high gradient in the absence of severe AS. This is a limitation of our study.

The results from our study showed that the prevalence of AS was 18%. The prevalence of severe AS was 2%, moderate AS 6% and mild AS 10%. Echocardiography was more sensitive than electrocardiography in detecting LV hypertrophy in our patients with AS.

The intensity and maximal location of the aortic systolic ejection murmur, transmission of the aortic systolic ejection murmur to the right carotid artery, and presence of an aortic ejection click did not differentiate between mild, moderate and severe AS. Prolonged duration of the aortic systolic ejection murmur, late peaking of the aortic systolic ejection murmur, prolonged carotid upstroke time, absent aortic second sound, and decreased or absent aortic second sound occurred more frequently in patients with severe or moderate AS than in patients with mild AS; but, these physical signs did not distinguish between severe and moderate AS.

TABLE II Correlation of Physical Signs of Valvular Aortic Stenosis with the Severity of Aortic Stenosis

Physical Sign	Severity of Aortic Stenosis		
	Mild	Moderate	Severe
	No. (%)	No. (%)	No. (%)
Prolonged duration ASEM*	2/70 (3)	31/49 (63)	16/19 (84)
Late peaking ASEM*	2/70 (3)	31/49 (63)	16/19 (84)
Prolonged carotid upstroke time*	2/74 (3)	16/49 (33)	10/19 (53)
A ₂ absent†	0/74 (0)	5/49 (10)	3/19 (16)
A ₂ decreased or absent*	4/74 (5)	24/49 (49)	14/19 (74)

A₂ = aortic second sound; ASEM = aortic systolic ejection murmur.

* p < 0.001 comparing severe and moderate aortic stenosis with mild aortic stenosis.

† p < 0.005 comparing severe and moderate aortic stenosis with mild aortic stenosis.

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Mitral Regurgitation During B Bump of the Mitral Valve Studied by Doppler Echocardiography

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B-bump formation of the mitral valve, a plateau between the A and C points on the mitral valve M-mode echocardiogram, suggests a high left ventricular end-diastolic pressure.¹ However, what kind of mitral flow occurs during the B bump is not clear. We used Doppler echocardiography to assess whether mitral regurgitation (MR) occurs during the mitral valve B bump.

Subjects comprised 22 patients, 13 men and 9 women aged 24 to 82 years (mean 64), with a B bump on the mitral valve M-mode echocardiogram. Underlying heart diseases were dilated cardiomyopathy in 9, prior myocardial infarction in 9, hypertensive heart disease in 2, hypertrophic cardiomyopathy in 1 and severe MR due to chordal rupture in 1.

The severity of congestive heart failure was determined according to New York Heart Association

(NYHA) functional class. The cardiothoracic ratio was calculated. M-mode, 2-dimensional and Doppler echocardiography were performed with a commercially available instrument (Toshiba SSH 65A). Left ventricular diastolic dimension, left ventricular systolic dimension and left atrial dimension were measured, and the percent fractional shortening of the left ventricle was calculated.

The PQ interval was measured. The P to B bump interval was also measured, i.e., the interval from the onset of the P wave of the electrocardiogram to the onset of the B bump on the mitral valve M-mode echocardiogram.

Mitral inflow velocity was recorded from the apical 4-chamber view by pulsed-wave Doppler echocardiography, with the sample volume just behind the mitral valve cusps in the left atrium. Special attention was paid to the presence of any backward flow coinciding with the B bump, and the velocity of any backward flow detected was measured. Peak mitral inflow velocities during early diastole (E velocity) and during atrial systole (A velocity) were measured and the A/E ratio was calculated.

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TABLE I Patient Profiles

Age (yr) & Sex	DX	BMR (LD)	BMR (PEP)	SMR	NYHA	CTR %	PQ (s)	P to B Bump (s)	LVDd (mm)	LVDs (mm)	LAD (mm)	E (cm/s)	A (cm/s)
Group A (n = 18)													
24 F	DC	(0)	(+)	III	III	49	0.17	0.21	69	65	33	55	46
47 M	DC	(+)	(+)	I	IV	44	0.32	0.20	60	46	32	29	41
63 F	DC	(0)	(+)	I	II	59	0.20	0.23	52	40	53	29	23
63 M	DC	(0)	(+)	I	III	61	0.19	0.24	64	57	47	44	26
76 F	DC	(0)	(+)	I	III	62	0.18	0.18	63	51	53	63	65
77 M	DC	(+)	(+)	I	III	60	0.22	0.19	75	67	51	63	53
66 M	MI	(+)	(+)	II	II	52	0.23	0.19	63	46	37	64	80
70 F	MI	(0)	(+)	I	III	53	0.20	0.20	56	47	40	57	35
72 F	MI	(+)	(+)	II	III	67	0.23	0.20	70	55	33	40	48
75 M	MI	(+)	(+)	II	III	57	0.23	0.20	68	54	47	55	25
75 M	MI	(+)	(+)	I	II	63	0.21	0.20	52	37	40	33	45
76 F	MI	(0)	(+)	II	II	56	0.20	0.20	54	43	39	38	31
76 M	MI	(0)	(+)	II	III	67	0.19	0.20	58	52	43	79	34
82 M	MI	(+)	(+)	I	III	65	0.24	0.21	56	43	32	58	40
72 F	HHD	(+)	(+)	I	I	58	0.26	0.20	56	40	39	56	59
77 M	HHD	(+)	(+)	I	II	54	0.25	0.20	51	46	46	50	58
71 M	MR	(+)	(+)	IV	III	53	0.26	0.19	69	40	56	99	33
43 M	HC	(+)	(+)	I	II	47	0.20	0.17	42	19	40	58	40
Group B (n = 4)													
47 M	DC	(0)	(0)	III	IV	58	0.19	0.25	75	69	55	67	22
51 F	DC	(0)	(0)	III	IV	61	0.20	0.23	65	55	54	96	25
51 M	DC	(0)	(0)	II	IV	65	0.23	0.22	67	58	56	58	16
64 F	MI	(0)	(0)	III	III	59	0.28	0.25	64	47	55	56	24

A = peak mitral flow velocity during atrial systole; BMR = mitral regurgitation during mitral valve B bump; CTR = cardiothoracic ratio; DC = dilated cardiomyopathy; DX = diagnosis; E = early diastolic peak mitral flow velocity; HC = hypertrophic cardiomyopathy; HHD = hypertensive heart disease; LAD = left atrial dimension; LD = late diastole; LVDd = left ventricular diastolic dimension; LVDs = left ventricular systolic dimension; MI = prior myocardial infarction; MR = mitral regurgitation; NYHA = New York Heart Association functional class; PEP = pre-ejection period; SMR = systolic mitral regurgitation.

Using a parasternal long-axis or apical view, a 2-dimensional color Doppler echocardiogram was recorded. Color red signals indicate "toward" flow and color blue signals indicate "away" flow. This 2-dimensional color Doppler echocardiogram was used to determine the presence of any blue signals behind the mitral valve coinciding with the B bump, or how far the blue signals progressed from the mitral valve orifice. An M-mode color Doppler echocardiogram was also recorded by placing the cursor on the mitral valve cusps. Special attention was paid to the detection of any blue signal behind the mitral valve coinciding with the B bump. We also used a 2-dimensional color Doppler echocardiogram for the detection of systolic MR. The severity of systolic MR was judged from the length of the systolic MR Doppler signal from the mitral valve orifice.²

All results are given as the mean \pm standard deviation. Differences between measurements were determined by a 2-tailed Student's *t* test. A *p* value <0.05 was considered statistically significant.

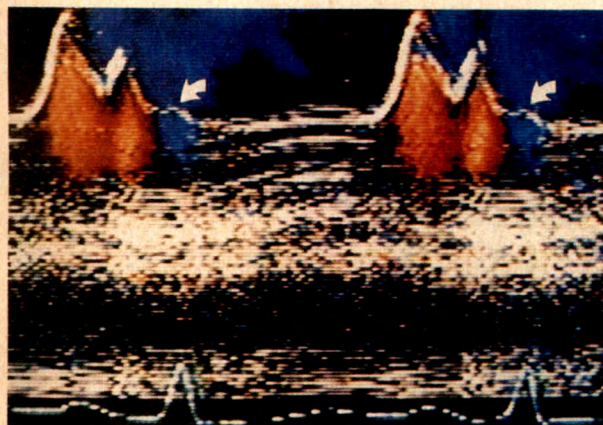


FIGURE 1. M-mode color Doppler echocardiographic detection of mitral regurgitation (white arrows) coincident with the B bump of the mitral valve. Mitral regurgitation is demonstrated as blue signals (white arrows) behind the mitral valve that coincide with the B bump.

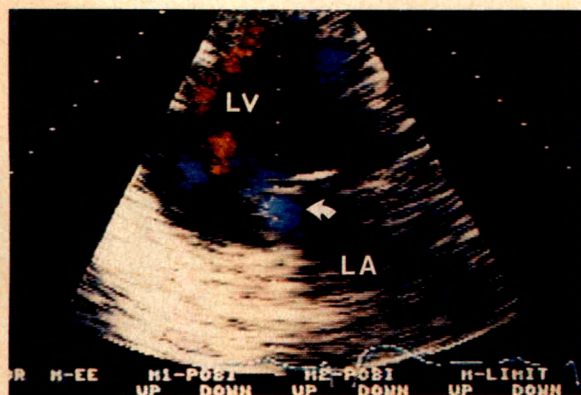


FIGURE 2. Mitral regurgitation (white arrow) coincident with the B bump of the mitral valve on a 2-dimensional color Doppler echocardiogram. Blue signals (white arrow) suggest regurgitant mitral flow because they are observed to travel from the mitral valve orifice into the left atrium (LA). LV = left ventricle.

Table 1 summarizes data for each patient. In 18 (group A) of the 22 patients (82%), blue signals behind the mitral valve, coinciding with the B bump, were observed on the M-mode color Doppler echocardiogram (Figure 1). In the other 4 patients (group B), the signal was not observed. On the 2-dimensional color Doppler echocardiogram, the blue signal was observed extending from the mitral valve orifice into the left atrium in all 18 patients (Figure 2). The length of this signal ranged from 0.7 to 1.8 cm (mean 1.3 ± 0.3 cm).

Pulsed-wave Doppler echocardiogram obtained from just behind the mitral valve cusps showed backward flow coincident with the B bump in 15 of the 22 patients (68%) (Figure 3), and its flow velocity ranged from 18 to 61 cm/s (mean 33 ± 10 cm/s).

The PQ interval ranged from 0.17 to 0.32 second. The P to B-bump interval ranged from 0.17 to 0.25 second. Consequently, 19 patients had a PQ interval within 0.20 second or a P to B-bump interval within 0.20 second. In 17 of the 19 patients, the blue signals were observed behind the mitral valve during the B bump. The PQ intervals were longer than the P to B-bump intervals in 11 of the 18 group A patients (Table 1).

There were no significant differences in age, cardiothoracic ratio, left ventricular diastolic or systolic dimension and percent fractional shortening of the left ventricle between groups A and B. NYHA functional class tended to be less severe in group A than in group B patients. The left atrial dimension in group A (42 ± 8 mm) was significantly smaller than that in group B (55 ± 1 mm, $p < 0.01$). The E velocity was not significantly different between the 2 groups, but the A velocity in group A (43 ± 15 cm/s) was significantly larger than that in group B (22 ± 4 cm/s, $p < 0.05$). The A/E ratio for group A (0.85 ± 0.31) was significantly larger than that for group B (0.33 ± 0.08 , $p < 0.01$). Systolic MR was detected in all subjects by 2-dimensional color Doppler echocardiography. In group A, the severity of systolic MR was grade I (mild) in 11 patients, grade II (mild to

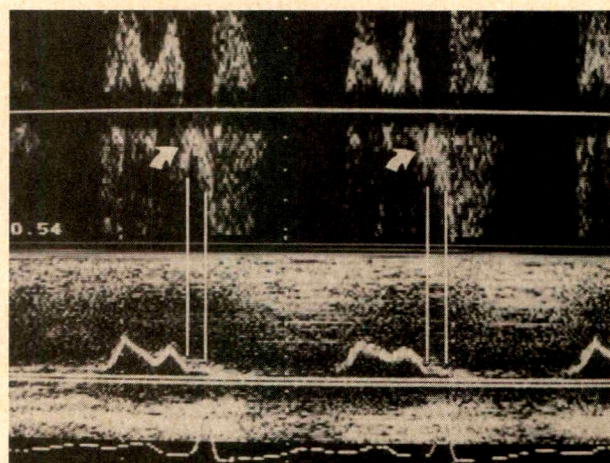


FIGURE 3. Pulsed-wave Doppler echocardiographic detection of mitral regurgitation (white arrows) coinciding with the B-bump formation of the mitral valve on the M-mode echocardiogram. Backward flows (white arrows) are shown to coincide with the mitral valve B bump.

moderate) in 5, grade III (moderate to severe) in 1 and grade IV (severe) in 1. In contrast, it was grade II in 1 and grade III in 3 patients in group B.

In the present study, blue signals behind the mitral valve were observed to coincide with the mitral valve B bump in most of the patients on M-mode or 2-dimensional color Doppler echocardiography. These blue signals represent flow away from the mitral valve orifice into the left atrium, thus indicating MR during B bump of the mitral valve.

MR coinciding with the B bump was observed during the preejection period in all 18 group A patients. In 11 of these, MR was also observed during late diastole. B bump is observed before the C point on the mitral valve M-mode echocardiogram.¹ Therefore, the preejection period, during which MR occurs, may not include the late portion of the preejection period, i.e., the interval from mitral valve closure to aortic valve opening.

Several kinds of atypical diastolic MR have been found in patients with atrioventricular block,³⁻⁵ aortic regurgitation,⁶⁻⁸ hypertrophic cardiomyopathy,⁹ severe MR^{7,10} and atrial septal defect.¹⁰ The MR studied herein was not associated with these aforementioned conditions in most of the patients. Therefore, MR during B bump is apparently different from those atypical diastolic MRs reported up to the present. This study indicates that B bump of the mitral valve is a new condition associated with MR.

MR coinciding with the B bump is unique because the mitral valve remains open during the regurgitation.¹ As to why the mitral valve remains open while blood flows from the left ventricle into the left atrium—we suggest that the pressure gradient between the ventricle and atrium is very small, sufficient for MR but not large enough for mitral valve closure.

The Doppler signals of MR during the B bump on the 2-dimensional color Doppler echocardiogram were localized near the mitral valve orifice in the left atrium and its flow velocity was generally low. Therefore, the regurgitant flow volume is small and its hemodynamic influence may be little.

Sensitivity of pulsed-wave Doppler echocardiography for detecting MR during the B bump was lower than that

of M-mode or 2-dimensional color Doppler echocardiography. This difference was probably due to technical factors.

NYHA functional classes of congestive heart failure and systolic MR tended to be severer in group B than group A patients. The left atrial dimension was significantly larger and the mitral inflow A velocity significantly less in group B patients. The lower A velocity in group B patients may imply a stiffer left ventricle, probably exceeding the left atrial ability to empty normally in late diastole.¹¹ In group B patients, MR during mitral valve B bump may not occur, presumably because reversed pressure gradient cannot take place because of a higher left atrial pressure.

In conclusion, mitral regurgitation may occur frequently during the mitral valve B bump.

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Aortic Aneurysm in Patients with Functionally Normal or Minimally Stenotic Bicuspid Aortic Valve

Roman T. Pachulski, MD, Anthony L. Weinberg, MB, and Kwan-Leung Chan, MD

Bicuspid aortic valve (BAV) is the most common form of congenital valvular disease, with a prevalence of approximately 1 to 2% in the general population.¹ Aortic coarctation is often associated with BAV.¹ A recent editorial by Lindsay² has drawn attention once again to the concept that BAV and aortic coarctation may be manifestations of a single developmental anomaly—namely, aortic medial fragility. This idea was initially proposed by Abbot³ in 1928, revived by McKusick⁴ in 1972, and supported by circumstantial evidence referred to by Lindsay in his editorial. To prove that aortic medial fragility underlies BAV and aortic coarctation, one must demonstrate the presence of a pathologic or clinical correlate of aortic medial fragility in patients with the index conditions. The proposed pathologic correlate, cystic medial necrosis, is nonspecific. The clinical correlates of aortic medial fragility include aortic dilatation (aneurysm) or dissection. Although the data cited by Lindsay are suggestive of an increased prevalence of aortic dilatation/dissection with BAV and coarctation, they could be expressions of the hemodynamic alterations accompanying the index conditions rather than manifestations of aortic medial fragility. To eliminate the confounding influence of hemodynamic disturbances, we studied the prevalence of aortic root dilatation (aneurysm) in patients with a functionally normal or minimally stenotic BAV. This study was to determine whether the aortic root at the sinus level is significantly dilated in patients with a functionally normal or minimally stenotic BAV, which we define as a resting mean aortic valve gradient <25 mm Hg, the absence of anything more than trivial aortic regurgitation and no coarctation as determined by Doppler echocardiography.

Two-dimensional echocardiography is known to be a reliable (sensitivity 78%, specificity 96%) and accurate (93%) means of identifying BAV.⁵ We identified all patients with echocardiographic diagnoses of BAV over a 41-month period from November 1985 to March 1989. We then identified an age- and sex-matched control group of 50 patients with normal echocardiograms during that same interval. Although 144 patients with BAV were initially identified, 17 were excluded because of greater than trivial aortic regurgitation, 14 because of aortic coarctation, 11 because of mean resting aortic gradients >25 mm Hg (continuous-wave Doppler) and 1 because of combined aortic stenosis and regurgitation,

leaving a study group of 101 patients with a functionally normal or minimally stenotic BAV.

Figure 1 indicates the conventional sites for aortic root diameter measurement.⁶ Our measurements were taken at the sinus level at end diastole. Measurements for the other levels were not consistently reported. Figure 2 shows the mean aortic root diameter measurements at the sinus level for patients with a functionally normal or minimally stenotic BAV and for control subjects. The mean aortic root diameter in patients with a functionally normal or minimally stenotic BAV was 35.2 ± 6.5 mm (range 20.0 to 54.0 mm), whereas the mean aortic root diameter in the control group was 30.4 ± 3.9 mm (range 23.0 to 40.0 mm). Analysis with Student's unpaired *t* test revealed this difference to be statistically highly significant ($p < 0.0001$). Furthermore, 58% of the study group and only 20% of control subjects had aortic root diame-

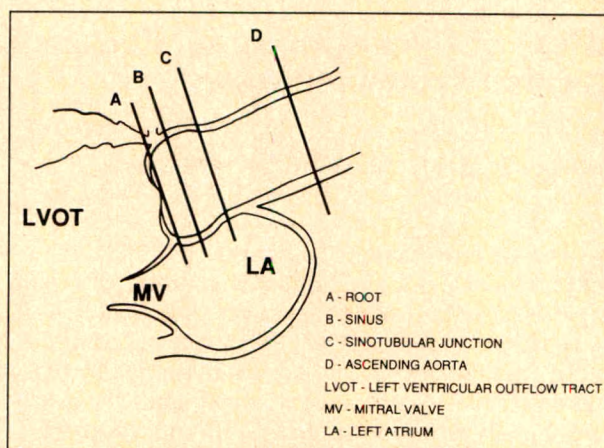


FIGURE 1. Conventional sites for aortic root diameter measurement.

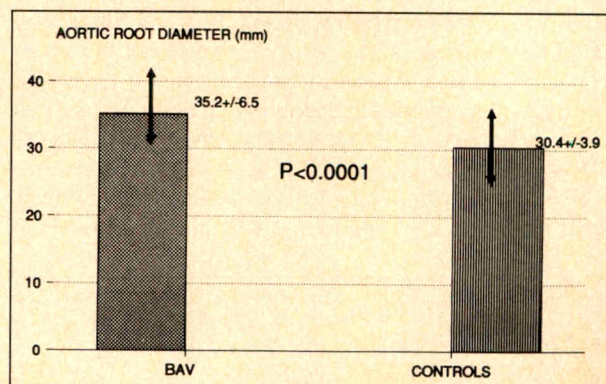


FIGURE 2. Mean aortic root diameter measurements at the sinus level for patients with a functionally normal or minimally stenotic bicuspid aortic valve (BAV) and for control subjects.

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ters >34 mm, a conventionally accepted upper limit of normal for the aortic root at the sinus level in adults.⁶

From the aforementioned findings we conclude that aortic dilatation is present in patients with a functionally normal or minimally stenotic BAV when compared with age- and sex-matched control subjects. It might be argued that lesser (<25 mm Hg) transvalvular pressure gradients or eccentric left ventricular stroke volume expulsion in the absence of a pressure gradient could cause aortic root dilatation. This is unlikely to account for the observed differences, because disturbances of flow at the valvular level tend to cause aortic root changes distal to the sinotubular junction. Our measurements were purposefully taken proximally, at the sinus level, to avoid this problem. Mean transvalvular pressure gradients <25 mm Hg at rest were recorded too infrequently (<5 patients) in our sample to attempt any reliable correlation between gradient magnitude and aortic root dimension. Cardiac catheterization data were not available. Although valve cusp eccentricity is acknowledged to occur in approximately 78% of BAV patients,⁵ it is not clear that the degree of cusp excursion eccentricity is sufficient to alter the direction of transvalvular blood flow. To disprove

these hypotheses definitively, the study would have to be repeated prospectively (so that mean transvalvular gradients at rest would be recorded in all cases) in patients with BAV who do not exhibit eccentric cusp excursion (approximately 22%⁵) and who meet the criteria for functional normality. In the absence of such an onerous undertaking, we feel that our data provide further evidence that aortic dilatation (a clinical correlate of aortic medial fragility) is present in patients with a functionally normal or minimally stenotic BAV.

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Effect of Cyclosporine on Plasma Endothelin Levels in Humans After Cardiac Transplantation

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Since the introduction of cyclosporine in 1980, the 1-year survival rate after cardiac transplantation is now in excess of 80%.¹ Despite the success experienced with cyclosporine, considerable morbidity remains associated with its use. Renal insufficiency characterized by renal vasoconstriction occurs frequently and limits the use of the drug.² Hypertension occurs in >90% of cyclosporine-treated cardiac transplant recipients.³

In vitro cyclosporine damages endothelial cells, resulting in cell lysis and detachment.⁴ Endothelin represents a newly recognized polypeptide produced by vascular endothelium. Exogenous administration of endothelin results in intense renal and systemic vasoconstriction.⁵ Recently, investigators speculated that endothelin may mediate cyclosporine-induced hypertension and renal insufficiency.⁶

Recent studies in the rat⁷ using superpharmacologic doses of cyclosporine demonstrate cyclosporine-induced activation of plasma endothelin with an associated in-

crease in renal vascular resistance. Administration of endothelin antisera reversed the renal vasoconstriction. The effect of clinically relevant doses of cyclosporine on the activation of circulating endothelin in humans has not been evaluated.

The current study was designed to (1) investigate whether plasma endothelin is activated in cyclosporine- and non-cyclosporine-treated patients after cardiac transplantation, and (2) to determine if a correlation exists between plasma endothelin and systemic arterial pressure or serum creatinine after transplantation.

Studies were performed in 27 stable cardiac transplant recipients. Group 1 comprised 21 subjects who have undergone cardiac transplantation since 1980 and who were being treated with a cyclosporine-based immunosuppressive regimen. Group 2 comprised 6 patients transplanted before the introduction of cyclosporine who were receiving only prednisone and azathioprine as immunosuppressive therapy.

While subjects were in the seated position, 10 ml of venous blood was collected from the antecubital vein. Whole blood was centrifuged at 2,500 r.p.m. at 4°C. The plasma was stored in polypropylene tubes at -20°C until assayed. Extracted plasma endothelin was determined by specific radioimmunoassay using rabbit anti-endothelin antisera (RAS6901, Peninsula Laborato-

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ries, Belmont, California), as previously described.⁸ The recovery of the extraction procedure was 81%. Interassay and intraassay variations were 9 and 5%, respectively. The lower level of detectability of the assay is 0.5 pg/ml, with a range of 0.5 to 400 pg/ml.

Serum creatinine was assayed using a clinical creatinine analyzer. Arterial pressure was determined using a sphygmomanometer while the patient was in the seated position.

Comparison between groups was performed by Student's unpaired 2-tailed *t* test. Statistical significance was achieved at the *p* < 0.05 level. Results are expressed as mean \pm standard error.

The average age of subjects at the time of study was 45 ± 3 years in group 1 and 41 ± 6 years in group 2. The average time from transplant to study was 22 ± 7 months in group 1 and 147 ± 17 months in group 2. Nineteen of 21 subjects in group 1 were men, as were 5 of 6 subjects in group 2.

Eighteen of 21 (86%) cyclosporine-treated patients (group 1) and 1 of 6 (17%) non-cyclosporine-treated patients (group 2) required antihypertensive therapy.

Mean arterial blood pressure with therapy was 102 ± 4 mm Hg in group 1 and 96 ± 5 mm Hg in group 2 (difference not significant). Serum creatinine was greater in group 1 (1.4 ± 0.1 mg/dl) than in group 2 (1.0 ± 0.1 mg/dl, *p* < 0.05) (Figure 1A).

Plasma endothelin was 3.2 ± 0.3 pg/ml in group 1 and 4.1 ± 0.8 pg/ml in group 2 (Figure 1B). This value was not statistically different from that measured in 67 normal subjects (2.4 ± 0.3 pg/ml) and the values between the 2 transplant groups were not statistically different. Plasma endothelin did not correlate with blood pressure (Figure 2A) or serum creatinine (Figure 2B) in either group.

In this series of stable cardiac transplant recipients, plasma endothelin was not different between cyclosporine- and non-cyclosporine-treated patients. Circulating endothelin did not correlate with arterial pressure or serum creatinine.

The ability to study endothelin in non-cyclosporine-treated cardiac transplant patients provides unique data and allows one the potential to separate cyclosporine effects from more general changes that may occur after

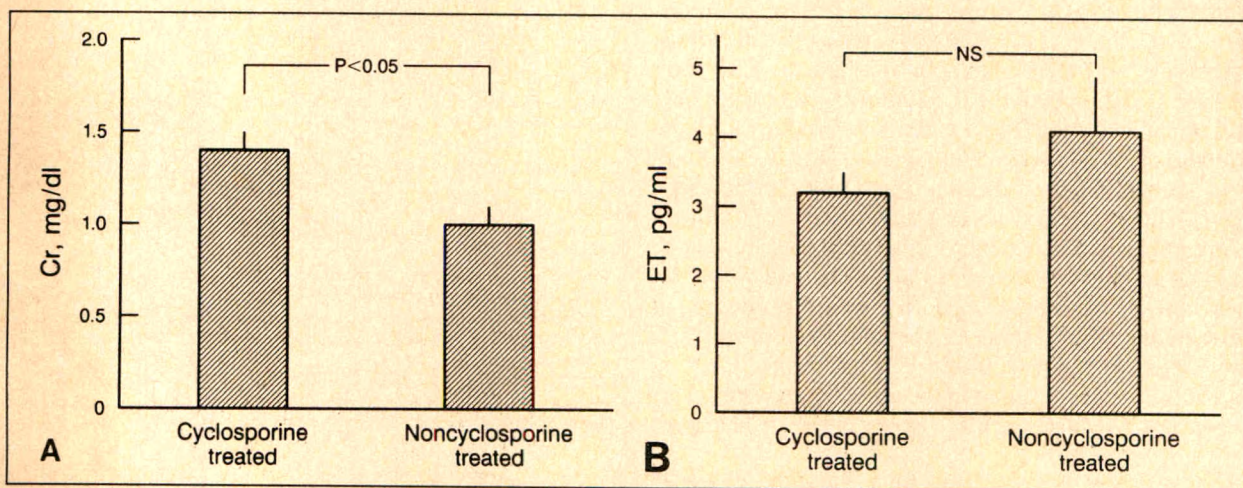


FIGURE 1. A, serum creatine (Cr), and B, plasma endothelin (ET) in cyclosporine- (n = 21) and non-cyclosporine-treated (n = 6) cardiac transplant recipients. NS = difference not significant.

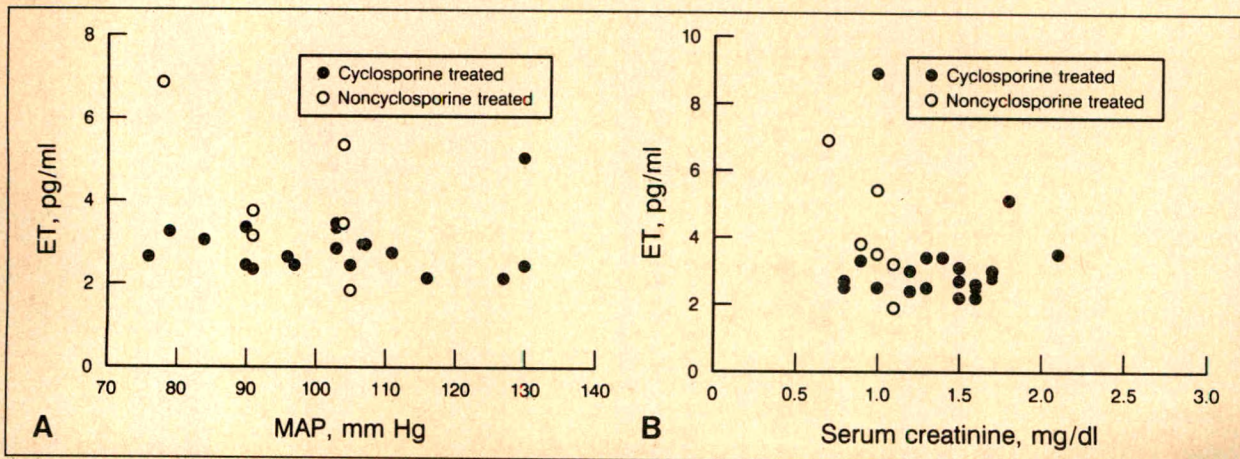


FIGURE 2. Relation between plasma endothelin (ET) and mean arterial pressure (MAP) (A) or serum creatinine (B). No significant correlation was observed.

cardiac transplantation. The fact that endothelin was not different between cyclosporine- and non-cyclosporine-treated patients provides unique evidence demonstrating that clinical levels of cyclosporine do not activate plasma endothelin.

The inability to document activation of endothelin in this large group of normotensive and hypertensive cardiac transplant recipients suggests several possible explanations. Although endothelin may not participate as a mediator for posttransplant hypertension and renal insufficiency, there are alternative possibilities. The sensitivity of the vasculature to endothelin may be altered by cyclosporine. Garr and Paller⁹ importantly demonstrated that cyclosporine may enhance the renal vascular response to a variety of vasoconstrictors. Potentially, in the cardiac transplant recipient treated with cyclosporine, there may be an enhanced vascular response to normal levels of endothelin. Furthermore, one cannot exclude the possibility of local endothelin action without significantly increasing circulating concentrations. In preliminary studies, Lerman et al¹⁰ observed that very low-dose endothelin (1 ng/kg/min) may increase renal vascular resistance without increasing plasma endothelin. Perico et al¹¹ recently demonstrated that cyclosporine may increase urinary endothelin excretion without altering plasma levels, suggesting intrarenal endothelin production. The distal nephron is rich in endothelin¹² and may potentially be a site for enhanced intrarenal endothelin production in the presence of cyclosporine. Finally, this study does not address the possibility of diurnal changes in plasma endothelin. In a preliminary observation, Grieff et al¹³ reported activation of plasma endothelin, which occurs 4 to 12 hours after ingestion of oral cyclosporine and which returns toward baseline as cyclosporine levels decline. In the current study, plasma endothelin was determined at a time when cyclosporine would be at a trough level.

Unlike previous studies in the rat using superpharmacologic doses of cyclosporine,⁸ the current study in human

cardiac transplant recipients demonstrates that chronic cyclosporine therapy is not associated with sustained activation of circulating endothelin. Furthermore, posttransplantation hypertension and renal insufficiency does not correlate with circulating endothelin and may occur in the absence of an increase in circulating endothelin.

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Usefulness of the Subaortic Diameter for Normalizing Left Ventricular and Left Atrial Dimensions

Michael J. Domanski, MD, Robert E. Cunnion, MD, and William C. Roberts, MD

Dimensions of the cardiac chambers and great arteries in the normal heart generally vary with cardiac size. To compare hearts of different sizes, it would be useful to normalize dimensions using a readily derived parameter that reflects normal or near normal heart size. Body surface area has been used but it is of limited value for this application.¹ This report examines the usefulness of the subaortic transverse diameter in the normalization of left ventricular (LV) end-diastolic and left atrial (LA) sizes.

Thirty-nine subjects, 15 men and 24 women, aged 4 to 49 years (mean 26), were studied. Group A (10 subjects) comprised children <12 years old with normal echocardiograms. Group B (21 subjects) comprised adults aged 21 to 49 years with normal echocardiograms. Group C (8 subjects) comprised adults aged 22 to 45 years with enlarged LV cavities (>56 mm in transverse dimension). Echocardiography was performed using a Hewlett-Packard Sonos 1000 or Sonos 500 imaging system. M-mode measurements of the LV end-diastolic dimension and LA size were performed as prescribed by the American Society of Echocardiography.² The inner edge to inner edge subaortic diameter was measured from the parasternal long-axis cross-sectional echocardiographic images immediately caudal to the base of the aortic

valve cusps (Figure 1). Values are expressed as mean \pm standard deviation; comparisons between groups were made using a 2-tailed Student's *t* test.

Table I lists data from each patient. Table II lists the mean values of groups A and B. Figure 2 displays LV end-diastolic dimension/subaortic diameter and LA size/subaortic diameter as a function of age. Although statistically significant differences existed for subaortic

TABLE I Echocardiographic Measurements in 39 Subjects with Normalized Values Using the Subaortic Diameter

Age (Years)	Sex	Subaortic Diameter (mm)	LVEDD (mm)	LA Size (mm)	LVEDD/ Subaortic Diameter	LA Size/ Subaortic Diameter
Group A: Children (n = 10)						
4	F	14	33	24	2.29	1.66
6	M	18	42	24	2.49	1.36
7	M	21	38	24	1.84	1.16
8	M	16	38	29	2.38	1.81
8	M	17	44	26	2.53	1.49
10	M	16	36	27	2.19	1.65
10	M	19	38	28	2.02	1.49
12	F	20	46	30	2.30	1.50
12	M	18	42	33	2.28	1.79
12	M	19	40	32	2.13	1.70
Group B: Adults (n = 21)						
18	M	22	50	28	2.28	1.28
19	M	24	—	32	—	1.33
23	F	19	46	39	2.39	2.03
24	F	19	46	29	2.37	1.49
25	F	22	51	38	2.31	1.72
25	F	22	—	30	—	1.39
27	F	19	40	33	2.14	1.76
29	F	20	44	36	2.17	1.77
30	F	18	51	31	2.79	1.69
30	F	23	50	32	2.22	1.42
32	F	21	53	36	2.48	1.68
33	F	19	—	35	—	1.81
34	F	19	46	26	2.47	1.40
34	F	19	44	34	2.28	1.76
34	M	22	54	35	2.43	1.58
35	F	19	46	25	2.38	1.29
36	F	18	45	30	2.49	1.66
39	F	18	40	36	2.19	1.97
43	F	19	50	30	2.63	1.58
44	F	19	42	30	2.22	1.59
49	F	22	45	30	2.07	1.38
Group C: Adults with increased LVEDD (n = 8)						
22	F	19	62	41	3.35	2.16
27	M	24	58	—	2.47	—
29	F	22	59	—	2.72	—
36	F	21	60	42	2.88	2.02
36	M	25	64	39	2.57	1.57
39	F	21	59	43	2.85	2.08
44	M	23	60	52	2.64	2.29
45	M	25	60	39	2.39	1.55

LA = left atrial; LVEDD = left ventricular end-diastolic dimension.

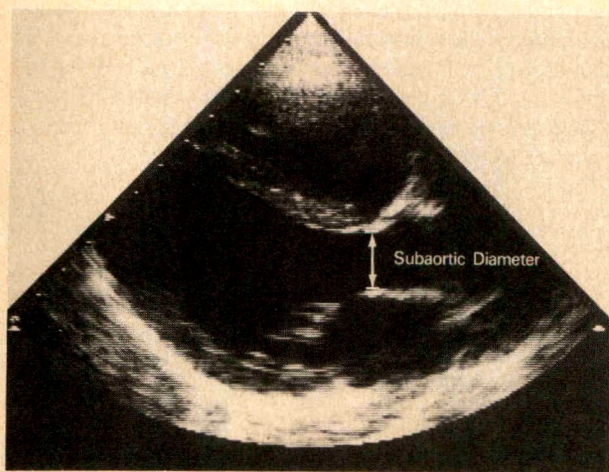


FIGURE 1. Parasternal long-axis cross-sectional echocardiographic image, showing measurement of the subaortic diameter.

TABLE II Echocardiographic Measurements with Normalized Values Using the Subaortic Diameter in Children Compared with Adults

Measurement	Children (Group A, n = 10)	Adults (Group B, n = 21)	p Value
Subaortic diameter (mm)	17.9 ± 1.9*	20.3 ± 1.7	<0.001
LVEDD (mm)	39.7 ± 3.9	46.8 ± 4.2	<0.001
LA size (mm)	27.7 ± 3.3	32.1 ± 3.8	<0.01
LVEDD/subaortic diameter	2.25 ± 0.21	2.34 ± 0.16	NS
LA size/subaortic diameter	1.56 ± 0.20	1.59 ± 0.21	NS

* Values are given as mean ± standard deviation.

LA = left atrial; LVEDD = left ventricular end-diastolic dimension; NS = difference not significant.

diameter, LV end-diastolic dimension and LA size in the children compared with adults, these differences were not present when LV end-diastolic dimension and LA size were normalized by dividing by the subaortic diameter.

In this study the subaortic diameter was used to normalize other cardiac dimensions. The nearly identical normalized values in children and adults reflect the constancy of these measurements in normal hearts. No differences in any values (LV end-diastolic dimension, LA size, subaortic diameter, LV end-diastolic dimension/subaortic diameter or LA size/subaortic diameter) were observed among the normal adults in this study as a function of age. Thus, both LV and LA dilatation were reflected as an alteration in the normalized values. Group C subjects were selected on the basis of an increased LV end-diastolic dimension. In all group C subjects whose subaortic diameter was normal ($\leq 1\frac{1}{2}$ standard deviations from group B subjects), the values of LV end-diastolic dimension/subaortic diameter were abnormal ($\leq 1\frac{1}{2}$ standard deviations from group B subjects). Similarly, all group C subjects with normal subaortic diameters and abnormal (>40 mm) LA sizes had abnormal LA size/subaortic diameter ($\leq 1\frac{1}{2}$ standard deviations from group B subjects) ratios. If the aortic root diameter is abnormal, however, the subaortic diameter may not adequately reflect normal heart size and it may not be an appropriate parameter for normalizing LV end-diastolic dimension and LA size. The range of the subaortic diameter derived from the group B subjects in this study (20.3 ± 1.7 mm) is similar to that reported by Weyman (21 ± 3).³

Body surface area is another parameter that has been used to normalize cardiac chamber dimensions. The substantial scatter present limits its usefulness.⁴ By comparison, the subaortic diameter is easily measured echocardiographically and is a convenient internal reference of heart size.

In conclusion, the constant proportions of LV end-diastolic dimension/subaortic diameter and LA size/sub-

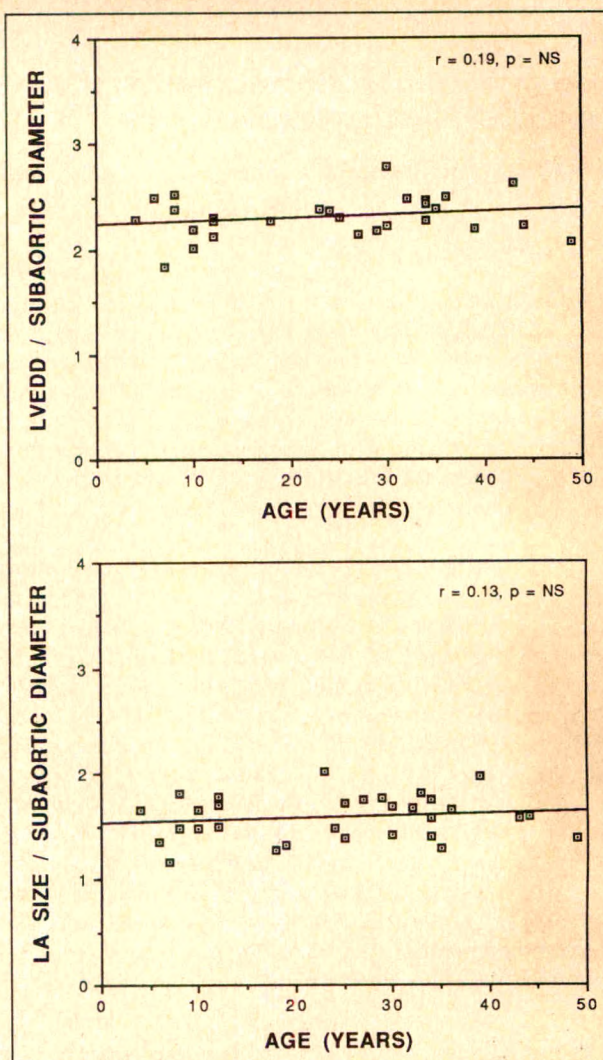


FIGURE 2. Graphs displaying, as a function of age, the ratios of left ventricular end-diastolic dimension (LVEDD) to subaortic diameter and of left atrial (LA) size to subaortic diameter for each patient. These ratios do not change with age up to 50 years. NS = difference not significant.

aortic diameter in the normal heart and the usual lack of variance of the subaortic diameter with disease make this dimension a convenient and effective parameter for normalizing LV end-diastolic dimension and LA size. If, however, the subaortic diameter is abnormally large or small, this technique is not reliable.

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Complications of Diagnostic Cardiac Catheterization Requiring Surgical Intervention

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Percutaneous cardiac catheterization for the diagnosis of cardiac disease has now become a routine and safe procedure with widespread application. Rarely, however, complications do occur that require emergency surgical intervention. The results of immediate surgical exploration are usually good; however, the long-term follow-up of these patients is unknown. This study reviews our experience with surgery for complications of cardiac catheterization and the long-term follow-up.

The records of all patients undergoing operation for complications of cardiac catheterization were retrospectively reviewed during the 5-year period from January 1984 to January 1989. There were 7,796 catheterizations (0.3%) performed, and 22 patients who required surgical intervention. All catheterizations were done through an 8Fr sheath with full heparinization. Ninety percent of patients were accessed through the femoral approach and the remaining were accessed through the brachial artery. The brachial artery route was chosen when femoral catheterization was unsuccessful.

All patients undergoing cardiac catheterization were admitted to the hospital and followed daily. There were no false aneurysms that were treated conservatively. Many patients with hematomas were seen and followed conservatively; however, any suggestion of a pulsatile mass was considered a false aneurysm and was surgically explored. We do not know if any patient with a vascular complication was seen and treated at another institution after discharge from the hospital; however, because of the nature of the referral base of our practice, it is unlikely that they were seen elsewhere.

Of the 22 patients requiring surgical interventions for complications of the cardiac catheterization, all initial cardiac catheterizations were diagnostic; none of the patients was undergoing thrombolytic therapy and none was on an intraaortic balloon pump.

The ideal weights for each patient were determined by standard charts for height, sex and age. The percentage over or under ideal weight for each patient was then determined.

Follow-up was determined by a telephone conversation or physical examination of the patient, or both. Physical examination included determinations for distal pulses, leg swelling, leg pain, neurologic complaints and incisional pain.

The age of the 22 patients ranged from 39 to 79 years (mean 65). The male to female ratio was 14 to 9. Age, sex, blood loss or history of hypertension had no relation to the type or location of the injury. The common femoral artery was the most common site of injury (14 of 22). Complications included 13 pseudoaneurysms, 5 arterial thromboses, 2 hematomas and 2 embolic events.

There was no correlation between the type of complication and the location of the arterial puncture. The type of anesthesia (local versus general) had no correlation with outcome. There was no correlation between the amount of blood loss at surgery and the time interval from catheterization to surgical repair. However, repair of the injury was technically more difficult the longer the time interval from the initial catheterization.

One patient (0.01%) lost his leg as a result of multiple tibial and pedal arterial emboli sustained during catheterization. Most patients (18 of 22) sustaining complications were $\geq 20\%$ over their appropriate weight.

At follow-up, two-thirds of patients were free of symptoms. The remaining patients complained of chronic leg pain, medial thigh anesthesia or incisional pain. No patient had a change in their circulatory status.

The results of our study compared favorably with recent reports of complications (1 to 5%).¹⁻⁵ Our most frequently seen complication was pseudoaneurysm formation (60%). Pseudoaneurysm usually occurs if the catheterization site fails to seal, leading to chronic leakage of blood into the surrounding tissues. Because 80% of our patients were overweight, we believe that pseudoaneurysm occurred most often as a result of inadequate compression after catheterization. Some surgeons recently suggested that pseudoaneurysms can be managed conservatively because most will eventually clot.

We have found that patients are symptomatically much improved after pseudoaneurysm repair and continue to advise aggressive surgical repair of lesions >4 centimeters in size. Repair of pseudoaneurysms are technically more difficult the longer the time interval from catheterization because of the increased inflammatory response. We recommend elective repair of these lesions shortly after the diagnosis is made.

Although we only evacuated 2 hematomas, many small hematomas were not surgically evacuated. Evacuation of hematomas below the inguinal ligament is difficult; the blood dissects into the muscular tissue planes and is difficult to remove. Hematomas in the retroperitoneum are more dangerous, however, as they tend to continue to bleed because of inadequate tissue compression. In contrast to previous reports,^{6,7} neither the amount of blood loss nor the time interval between catheterization and surgery correlated with morbidity.

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Thromboses and embolic events constitute a true surgical emergency, as ischemia time is directly correlated with major limb morbidity and mortality. These patients should be given 5,000 U of intravenous heparin immediately and surgically explored as soon as possible.

At follow-up, two-thirds of the patients were free of symptoms related to the surgical procedures. To our surprise, one-third complained of significant chronic leg pain, medial thigh anesthesia or incisional pain. No patient had chronic leg swelling or arterial insufficiency as a direct result of the procedure.

The results of this study indicate that cardiac catheterization is very safe. When the rare complication does occur, it usually can be corrected safely with immediate operation, under local anesthesia, and without a preoperative angiogram. Although operation prevents limb loss in most cases, a significant number of patients will have

chronic complaints related to the surgical repair of these lesions.

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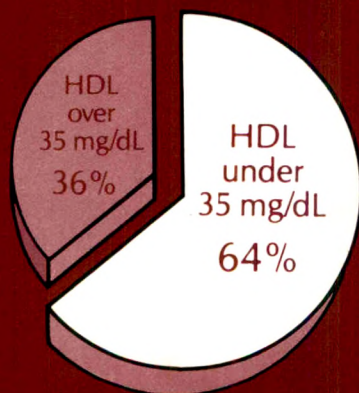
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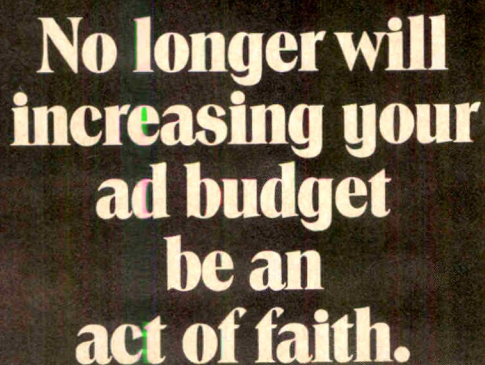
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CORONARY ARTERY DISEASE**789****An Economic Evaluation of Lovastatin for Cholesterol Lowering and Coronary Artery Disease Reduction**

Joel W. Hay, Ellison H. Wittels, and Antonio M. Gotto, Jr.

The costs and benefits of cholesterol lowering in primary prevention of coronary artery disease were considered using lifetime lovastatin therapy as the intervention model for adults between 35 and 55 years of age. The results were more favorable than those found in previous studies of alternate medication therapies for hypercholesterolemia. At least 800,000 Americans aged 35 to 55 years are at sufficiently high risk for CAD, so that the net cost of lovastatin therapy can be favorably compared to other widely used interventions.

797**Effects of Time Required for Reperfusion (Thrombolysis or Angioplasty, or Both) and Location of Acute Myocardial Infarction on Left Ventricular Functional Reserve Capacity Several Months Later**

Thomas Little, Marshall Crenshaw, Henry A. Liberman, Louis L. Battey, Robert Warner, André L. Churchwell, Robert L. Eisner, Douglas C. Morris, and Randolph E. Patterson

To test whether early reperfusion (≤ 4.5 hours) with recombinant tissue-type plasminogen activator or angioplasty, or both, would improve left ventricular ejection fraction during exercise in patients studied several months after acute myocardial infarction, radionuclide angiography and thallium-201 imaging were performed in 44 patients 5 months (6 weeks to 9 months) after AMI. Global LV function and functional reserve during exercise were both improved by early reperfusion in patients with an anterior wall but not an inferior wall AMI.

806**Frequency and Significance of Occult Late Potentials on the Signal-Averaged Electrocardiogram in Sustained Ventricular Tachycardia After Healing of Acute Myocardial Infarction**

Pramod Deshmukh, Stephen L. Winters, and J. Anthony Gomes

The signal-averaged electrocardiograms of 48 patients with sustained ventricular tachycardia after healing of acute myocardial infarction were analyzed. It is concluded that morphologic types of late potentials are likely a function of the anatomic and geometric differences within the substrate, with resultant differences in conduction.

812**Usefulness of the Automatic Implantable Cardioverter Defibrillator in Improving Survival of Patients with Severely Depressed Left Ventricular Function Associated with Coronary Artery Disease**

Eduardo de Marchena, Simon Chakko, Pedro Fernandez, Augusto Villa, Debbie Cooper, Paula Wozniak, Jose Cruz, Richard J. Thurer, Kenneth M. Kessler, and Robert J. Myerburg

To determine the effect of the automatic implantable cardioverter defibrillator on survival, investigators analyzed the demographic characteristics of 39 consecutive patients (29 survivors of out-of-hospital cardiac arrest and 10 with drug-refractory ventricular tachycardia; mean age 64 years) followed for a mean of 24 months after AICD implantation. The difference between actual and projected survival rates—with projections based on data of patients who survived without appropriate AICD discharge—was statistically significant, suggesting that the AICD improves the chances of survival in patients with severely depressed left ventricular function associated with coronary artery disease.

Comparison of Intravascular Ultrasound, External Ultrasound and Digital Angiography for Evaluation of Peripheral Artery Dimensions and Morphology

Khalid H. Sheikh, Charles J. Davidson, Katherine B. Kisslo, J. Kevin Harrison, Stevan I. Himmelstein, Joseph Kisslo, and Thomas M. Bashore

To further validate the accuracy of the catheter-based intravascular ultrasound technique in the determination of arterial dimensions and morphology, vascular images of the femoral artery system at 29 sites in 15 patients were obtained by intravascular ultrasound, 2-dimensional external ultrasound, Doppler color-flow imaging and digital angiography. Data indicate that dimensions determined by intravascular ultrasound correlate well with both external ultrasound and angiography in normal and minimally diseased peripheral arteries, but that angiography often yields results discordant with both intravascular and external ultrasound in the detection of the presence and composition of plaque.

823

Left Ventricular Diastolic Function in Patients with Left Ventricular Systolic Dysfunction Due to Coronary Artery Disease and Effect of Nicardipine

Constantine N. Aroney, Marc J. Semigran, G. William Dec, Charles A. Boucher, and Michael A. Fifer

To assess the effect of nicardipine on left ventricular diastolic function independent of changes in loading conditions, equihypotensive doses of intravenous nitroprusside and nicardipine were administered to 12 patients with LV systolic dysfunction due to coronary artery disease. Nicardipine did not offer an advantage over nitroprusside with regard to acute effects on diastolic function.

ARRHYTHMIAS AND CONDUCTION DISTURBANCES

830

A New Method for Estimating Preexcitation Index Without Extrastimulus Technique and Its Usefulness in Determining the Mechanism of Supraventricular Tachycardia

Takeshi Yamashita, Hiroshi Inoue, Akira Nozaki, Tsong-Teh Kuo, Masahiro Usui, Shinichiro Saihara, and Tsuneaki Sugimoto

To test whether a preexcitation index, useful in determining the mechanism of paroxysmal supraventricular tachycardia and the site of the accessory pathway in atrioventricular reentrant tachycardia, could be computed analytically instead of by scanning the whole SVT

cycle with extrastimuli, 19 patients with SVT were divided into 2 groups: 15 whose preexcitation index could and 4 whose preexcitation index could not be determined. In these 4, the authors' new index was able to differentiate AV reentrant tachycardia from AV nodal reentrant tachycardia. The new index is helpful in determining the mechanism of SVT, even when retrograde atrial preexcitation by a ventricular extrastimulus does not occur.

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Usefulness of the Electrophysiology Laboratory for Evaluation of Proarrhythmic Drug Response in Coronary Artery Disease

Alfred E. Buxton, Mark E. Rosenthal, Francis E. Marchlinski, John M. Miller, Belinda Flores, and Mark E. Josephson

Two potential manifestations of proarrhythmic response to type IA antiarrhythmic agents—conversion of uniform nonsustained ventricular tachycardia to sustained VT and induction of sustained VT by fewer extrastimuli—were evaluated in 122 patients with chronic coronary artery disease and previous myocardial infarction after administration of procainamide. The authors conclude that it is premature to consider a decrease in the number of extrastimuli required to induce sustained VT after drug administration as a proarrhythmic drug effect.

843

Effectiveness of Glibenclamide on Myocardial Ischemic Ventricular Arrhythmias in Non-Insulin-Dependent Diabetes Mellitus

Federico Cacciapuoti, Renato Spiezia, Ugo Bianchi, Diana Lama, Maria D'Avino, and Michele Varricchio

Nineteen non-insulin-dependent diabetic patients were chosen for evaluation of the antiarrhythmic effects of glibenclamide, a hypoglycemic sulfonylurea. Results indicate that glibenclamide appears to be useful in treating ventricular ischemic arrhythmias.

CONGESTIVE HEART FAILURE

848

Incremental Prognostic Value of Exercise Hemodynamic Variables in Chronic Congestive Heart Failure Secondary to Coronary Artery Disease or to Dilated Cardiomyopathy

Brian P. Griffin, Prediman K. Shah, John Ferguson, and Stanley A. Rubin

Both resting and exercise hemodynamic measurements were used to predict 1-year survival in 49 patients with congestive heart failure. Data suggest that, among patients with CHF, a subset of patients with a very high 1-year mortality may be identified using hemodynamic

evaluation at rest and during exercise, and this information may be useful when selecting patients for cardiac transplantation.

VALVULAR HEART DISEASE

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Short- and Long-Term Results of Catheter Balloon Percutaneous Transvenous Mitral Commissurotomy

Jui-Sung Hung, Ming-Shyan Chern, Jong-Jen Wu, Morgan Fu, Kou-Ho Yeh, Yahn-Chyurn Wu, Wen-Jin Cherng, Sarah Chua, and Ching-Bin Lee

Percutaneous transvenous mitral commissurotomy for severe rheumatic mitral stenosis was successfully performed in 216 of 219 consecutive patients. PTMC is safe, achieves good immediate and long-term results, and is the procedure of choice in selected patients with mitral stenosis.

863

Effects of Aerobic Exercise Training on Symptomatic Women with Mitral Valve Prolapse

Kristine A. Scordo

Effects of a 12-week aerobic exercise training protocol were studied in 32 women with mitral valve prolapse. Levels of catecholamine did not change significantly at rest or during peak exercise. Findings support the use of aerobic exercise in the management of symptomatic women with MVP.

869

Validity of an Early Postoperative Baseline Doppler Recording After Aortic Valve Replacement

Rune Wiseth, Lars Hegrenaes, Ole Rossvoll, Terje Skjaerpe, and Liv Hatle

To assess the validity of the early postoperative pressure decrease across aortic valve prostheses as a baseline for later comparison, a Doppler ultrasound recording was obtained at a mean of 11 days after aortic valve replacement (51 bioprostheses, 78 mechanical) in 131 consecutive patients and again 3 to 5 months later. The authors suggest that a significant increase in mean pressure decrease between baseline and follow-up could indicate a leaky or obstructed valve, and that all patients undergoing aortic valve replacement should routinely undergo Doppler ultrasound before hospital discharge.

CONGENITAL HEART DISEASE

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Ventricular Late Potentials and Induced Ventricular Arrhythmias After Surgical Repair of Tetralogy of Fallot

Marc Zimmermann, Beat Friedli, Richard Adamec, and Ingrid Oberhänsli

Thirty-one asymptomatic patients with postoperative tetralogy of Fallot were prospectively studied to analyze results of programmed ventricular stimulation and the relation between inducible ventricular tachycardia and the presence of late potentials and spontaneous ventricular premature complexes. Shortly after repair of tetralogy of Fallot, the presence of spontaneous VPCs and ventricular late potentials are associated with an increased incidence of inducible VT. The absence of VPCs and late potentials may identify patients at low risk of subsequent ventricular arrhythmias.

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Thallium-201 Stress Scintigraphy in Takayasu Arteritis

Yuji Hashimoto, Fujio Numano, Yoshiaki Maruyama, Toshiyuki Oniki, Kenji Kasuya, Tsunekazu Kakuta, Tomoko Wada, Michiyoshi Yajima, and Hidenori Maezawa

Of 38 women with Takayasu arteritis who underwent thallium-201 stress myocardial scintigraphy, 20 (53%) had abnormal perfusion defects—permanent in 6, reversible in 7, and slow washout in 7—responsible for their decreased coronary reserve or myocardial damage, or both, and likely the result of long-standing systemic hypertension or complicated aortic regurgitation. The authors recommend evaluating patients with Takayasu arteritis who have perfusion defects for the presence of coronary artery disease.

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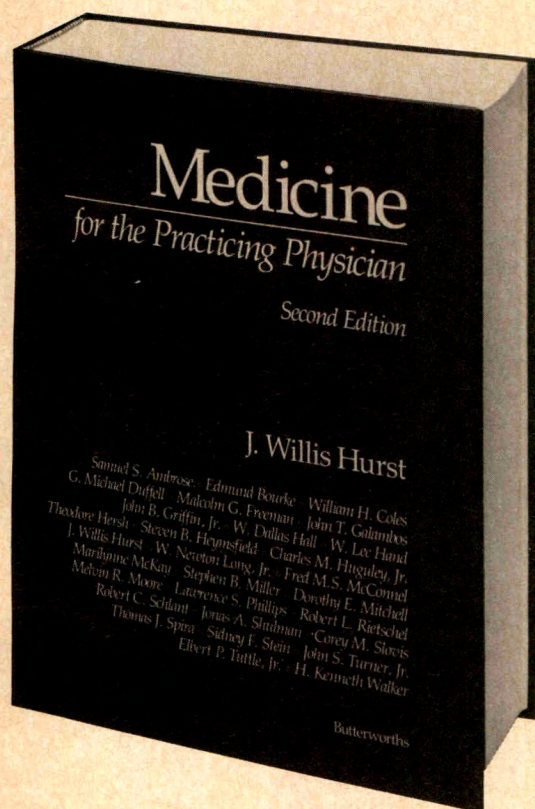
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CORONARY ARTERY DISEASE

789**An Economic Evaluation of Lovastatin for Cholesterol Lowering and Coronary Artery Disease Reduction**

Joel W. Hay, Ellison H. Wittels, and Antonio M. Gotto, Jr.

The costs and benefits of cholesterol lowering in the primary prevention of coronary artery disease (CAD) were considered using lifetime lovastatin therapy as the intervention model for adults between 35 and 55 years of age. For average-risk men with total serum cholesterol levels between 5.69 and 9.83 mmol/liter (220 and 380 mg/dl), the cost per life-year saved ranged from \$9,000 to \$106,000, whereas for average-risk women, the cost ranged from \$35,000 to \$297,000 (1989 U.S. dollars). In high-risk men (with smoking habit and hypertension), the cost per life-year saved values ranged from \$6,000 to \$53,000, whereas in high-risk women, the cost per life-year saved values ranged from \$19,000 to \$160,000. The results were more favorable than those found in previous studies of alternate medication therapies for hypercholesterolemia. At least 800,000 Americans aged 35 to 55 are at sufficiently high risk for CAD, so that the net cost of lovastatin therapy can be favorably compared to other widely used medical interventions.

797**Effects of Time Required for Reperfusion (Thrombolysis or Angioplasty, or Both) and Location of Acute Myocardial Infarction on Left Ventricular Functional Reserve Capacity Several Months Later**

Thomas Little, Marshall Crenshaw, Henry A. Liberman, Louis L. Battey, Robert Warner, André L. Churchwell, Robert L. Eisner, Douglas C. Morris, and Randolph E. Patterson

The purpose of this study was to test whether early reperfusion with recombinant tissue-type plasminogen activator or angioplasty, or both, would improve left ventricular (LV) ejection fraction during exercise in patients studied several months after acute myocardial infarction (AMI). Reperfusion documented angiographically ≤ 4.5 hours after the onset of chest pain led to improved exercise and LV ejection fraction at rest in patients with an anterior AMI, compared with patients reperfused after 4.5 hours or not at all. In contrast, patients with an inferior AMI had no difference in rest or exercise LV ejection fraction with early reperfusion. Exercise tomographic thallium-201 revealed no evidence of myocardial

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ischemia several months after AMI, probably because of percutaneous transluminal coronary angioplasty or surgery, or both, performed to ensure optimal revascularization.

806

Frequency and Significance of Occult Late Potentials on the Signal-Averaged Electrocardiogram in Sustained Ventricular Tachycardia After Healing of Acute Myocardial Infarction

Pramod Deshmukh, Stephen L. Winters, and J. Anthony Gomes

The signal-averaged electrocardiograms of 48 patients with sustained ventricular tachycardia after healing of acute myocardial infarction were analyzed. Late potentials could be classified into 3 morphologic subtypes. Type I late potentials occurred in the terminal 40 ms of the QRS complex and were seen in 40% of patients. Type II late potentials started before the end of the QRS complex and extended 30 ± 17 ms into the ST segment and were seen in 33% of patients. Type III late potentials started at the end of the QRS complex and extended 67 ± 27 ms into the ST segment and were seen in 27% of patients. The amplitude of the late potentials in type III, when compared with types I and II, were significantly lower, whereas the QRS duration on the electrocardiogram was significantly longer in type I when compared with types I and III. No differences were noted in age, sex, site of myocardial infarction, or rate of induced VT between the 3 types. Computer algorithm based on noise failed to identify most type III late potentials. It is concluded that morphologic types of late potentials are likely a function of the anatomic and geometric differences within the substrate, with resultant differences in conduction. Type III late potentials, which were seen in 27% of patients with ventricular tachycardia after myocardial infarction, are often missed by computer algorithms based on noise, and therefore are better suited for qualitative analysis.

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Usefulness of the Automatic Implantable Cardioverter Defibrillator in Improving Survival of Patients with Severely Depressed Left Ventricular Function Associated with Coronary Artery Disease

Eduardo de Marchena, Simon Chakko, Pedro Fernandez, Augusto Villa, Debbie Cooper, Paula Wozniak, Jose Cruz, Richard J. Thurer, Kenneth M. Kessler, and Robert J. Myerburg

We analyzed the clinical outcome of 39 patients with coronary artery disease, severely depressed left ventricular (LV) function and previous potentially lethal arrhythmic events requiring the automatic implantable cardioverter defibrillator (AICD). Patients had characteristics that predicted a high mortality rate, including advanced age (mean 64 years) and a low mean LV ejection fraction of $21 \pm 4\%$. Nevertheless, actuarial survival was 77% at 1 year and 72% at 2 years, with a projected survival rate—without an AICD—of 30% at 1 year and 21% at 2 years; the difference between actuarial and projected survival was statistically significant. This study suggests that the AICD improves survival in patients with coronary artery disease, despite severely depressed LV function.

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Comparison of Intravascular Ultrasound, External Ultrasound and Digital Angiography for Evaluation of Peripheral Artery Dimensions and Morphology

Khalid H. Sheikh, Charles J. Davidson, Katherine B. Kisslo, J. Kevin Harrison, Stevan I. Himmelstein, Joseph Kisslo, and Thomas M. Bashore

Catheter-based intravascular ultrasound is a new vascular imaging technique. To further validate arterial dimensions and morphology determined by intravascular ultrasound, vascular images of the femoral artery system at 29 sites in 15 patients were obtained by intravascular ultrasound, external 2-dimensional ultrasound, Doppler color-flow imaging and digital angiography, and were compared for arterial dimensions and morphology. Arterial dimensions determined by intravascular ultrasound correlated well with all 3 imaging techniques (all $r > 0.90$). Intravascular ultrasound detected minor arterial plaque at 15 sites, 5 of which were hypoechoic (soft) and 10 hyperechoic with distal shadowing (hard). External 2-dimensional imaging noted plaque at 12 of 15 sites, whereas angiography noted plaque at only 6 of 15 sites, only 1 of which was thought to be calcified. These data indicate that arterial dimensions determined by intravascular ultrasound correlate well with both external ultrasound and angiography in normal and minimally diseased peripheral arteries. However, angiography is often discordant with both intravascular and external ultrasound in determining the presence and composition of plaque.

823

Left Ventricular Diastolic Function in Patients with Left Ventricular Systolic Dysfunction Due to Coronary Artery Disease and Effect of Nicardipine

Constantine N. Aroney, Marc J. Semigran, G. William Dec, Charles A. Boucher, and Michael A. Fifer

To assess the effect of nicardipine on left ventricular (LV) diastolic function independent of changes in loading conditions, we administered equipotensive doses of intravenous nitroprusside and nicardipine to 12 patients with LV systolic dysfunction due to coronary artery disease. LV micromanometer pressure and simultaneous radionuclide volume were measured. A greater decrease in LV end-diastolic pressure was observed with nitroprusside (29 ± 2 to 15 ± 2 mm Hg, $p < 0.01$) than with nicardipine (29 ± 2 to 25 ± 3 mm Hg, $p < 0.05$). There was a decrease in the time constant of relaxation with nitroprusside but not with nicardipine. There was enough overlap in LV volumes in the baseline and nitroprusside periods to compare diastolic pressure-volume relations over a common range of volumes in 4 patients, and enough overlap in the baseline and nicardipine periods in 11 patients. The relation was shifted downward in 3 of 4 patients taking nitroprusside and in 6 of 11 patients taking nicardipine. The relation between end-diastolic pressure and volume was not shifted with nicardipine. With regard to acute effects on diastolic function, nicardipine did not offer an advantage over nitroprusside in this patient group.

Continued on page A22

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ARRHYTHMIAS AND CONDUCTION DISTURBANCES

830

A New Method for Estimating Preexcitation Index Without Extrastimulus Technique and Its Usefulness in Determining the Mechanism of Supraventricular Tachycardia

Takeshi Yamashita, Hiroshi Inoue, Akira Nozaki, Tsong-Teh Kuo, Masahiro Usui, Shinichiro Saihara, and Tsuneaki Sugimoto

A new method for estimating the preexcitation index was studied in 19 patients with paroxysmal supraventricular tachycardia (SVT). Our index was computed analytically using the following formula: (atrioventricular [AV] conduction time during tachycardia) + (ventriculoatrial conduction time during ventricular pacing at the tachycardia cycle length) – (tachycardia cycle length). There was a strong correlation between the preexcitation index determined by the extrastimulus technique and our index. Our index was effective in determining the mechanism of SVT and the site of the accessory pathway in orthodromic AV reentrant tachycardia, and could be applied even when retrograde atrial preexcitation by a ventricular extrastimulus did not occur.

835

Usefulness of the Electrophysiology Laboratory for Evaluation of Proarrhythmic Drug Response in Coronary Artery Disease

Alfred E. Buxton, Mark E. Rosenthal, Francis E. Marchlinski, John M. Miller, Belinda Flores, and Mark E. Josephson

We evaluated 2 potential manifestations of proarrhythmic responses to procainamide in the electrophysiology laboratory in 122 patients with chronic coronary artery disease and prior myocardial infarction. Conversion of uniform nonsustained ventricular tachycardia (VT) into the same morphology of sustained VT after procainamide occurred in 10% of patients presenting with nonsustained VT and never in patients presenting with sustained VT. Induction of sustained VT by fewer extrastimuli after procainamide did not appear to be a marker for potential proarrhythmic drug effects.

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Effectiveness of Glibenclamide on Myocardial Ischemic Ventricular Arrhythmias in Non-Insulin-Dependent Diabetes Mellitus

Federico Cacciapuoti, Renato Spiezia, Ugo Bianchi, Diana Lama, Maria D'Avino, and Michele Varricchio

The adenosine triphosphatase–modulated potassium ion channel opening of the myocardial cells, induced by hypoxia, is a major cause of ischemic ventricular arrhythmias. Glibenclamide appears to be a potent blocker of these channels, both in pancreatic β cells and in myocardial fibers. In the present study, the antiarrhythmic effect of glibenclamide was evaluated in 19 non-insulin-dependent diabetic patients with coronary artery disease

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and 24-hour Holter evidence of ventricular tachyarrhythmias during transient myocardial ischemia. After continuous basal Holter monitoring, patients were randomly classified into 2 groups and treated with glibenclamide and metformin (placebo) following a crossover pattern. Results obtained suggest that glibenclamide appears to be an antiarrhythmic drug that is useful in treating ventricular ischemic arrhythmias.

CONGESTIVE HEART FAILURE

848

Incremental Prognostic Value of Exercise Hemodynamic Variables in Chronic Congestive Heart Failure Secondary to Coronary Artery Disease or to Dilated Cardiomyopathy

Brian P. Griffin, Prediman K. Shah, John Ferguson, and Stanley A. Rubin

Both resting and exercise hemodynamic measurements were used to predict 1-year survival in 49 patients with congestive heart failure. Mortality at 1 year was 33%. Pulmonary arterial wedge pressure and stroke work index were significant univariate predictors of survival both at rest and during exercise, whereas left ventricular ejection fraction, oxygen consumption, exercise duration or left ventricular hydraulic power did not predict survival. Patients with a peak exercise stroke work index of <20 g-m/m² had a 66% mortality rate compared with a mortality rate of 13% in patients with a peak stroke work index >20 g-m/m² ($p = 0.0001$). Multiple regression analysis identified resting pulmonary arterial wedge pressure and peak stroke work index as the only independent predictors of survival. A receiver-operating characteristic curve analysis revealed that peak exercise stroke work index provided significant incremental prognostic information over the resting hemodynamic variables.

VALVULAR HEART DISEASE

854

Short- and Long-Term Results of Catheter Balloon Percutaneous Transvenous Mitral Commissurotomy

Jui-Sung Hung, Ming-Shyan Chern, Jong-Jen Wu, Morgan Fu, Kou-Ho Yeh, Yahn-Chyurn Wu, Wen-Jin Cherng, Sarah Chua, and Ching-Bin Lee

Percutaneous transvenous mitral commissurotomy (PTMC) for severe rheumatic mitral stenosis was successfully performed in 216 of 219 consecutive patients, aged 19 to 76 years (mean 43). The procedure resulted in immediate hemodynamic improvements with an increase in mitral valve area from 1.0 ± 0.3 to 2.0 ± 0.7 cm² ($p = 0.0001$). The results mirrored clinical improvements of symptoms and exercise tolerance in 209 patients (97%). The only in-hospital death occurred in a premonitory patient days after emergency last-resort PTMC created 3+ mitral regurgitation. Severe 3+ mitral regurgitation resulted in 6%, systemic embolisms in 1.4%

Continued on page A31

and atrial septal defects in 15% of the patients. There was no cardiac tamponade or emergency surgery. The cardiovascular event-free survival rate for the patients with pliable, noncalcified mitral valves was 100% up to 42 months; for those with calcified valves or with severe subvalvular lesions, or both, it was 91% at 12 months, and held at 76% from 24 to 31 months. PTMC is safe, achieves good immediate and long-term results, and is the procedure of choice in selected patients with mitral stenosis.

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Effects of Aerobic Exercise Training on Symptomatic Women with Mitral Valve Prolapse

Kristine A. Scordo

The effects of a 12-week aerobic exercise training protocol on 32 symptomatic women with mitral valve prolapse were studied. After a 12-week (3 times per week) aerobic exercise training program, the exercise group had a significant decrease ($p < 0.05$) in State Trait Anxiety Inventory scores, an increase in General Well-Being scores, an increase in functional capacity and a decline in the frequency of chest pain, fatigue, dizziness and mood swings compared with the control group. No statistically significant differences were noted in resting or peak exercise catecholamines. These findings support the use of aerobic exercise in the management of symptomatic women with mitral valve prolapse.

869

Validity of an Early Postoperative Baseline Doppler Recording After Aortic Valve Replacement

Rune Wiseth, Lars Hegrenaes, Ole Rossvoll, Terje Skjaerpe, and Liv Hatle

In 131 patients undergoing aortic valve replacement, the transprosthetic pressure decrease obtained at an early postoperative baseline recording (mean 11 days) was compared with a repeat measurement 3 to 5 months later. Although the hemodynamic state differed markedly at the 2 examinations, with increased heart rate and decreased left ventricular ejection time at the baseline recording, the change in mean pressure decrease between the 2 examinations was within ± 5 mm Hg in 82% of the patients. Based on these data, a routine Doppler recording before discharge after aortic valve replacement is recommended as a baseline for later comparison.

CONGENITAL HEART DISEASE

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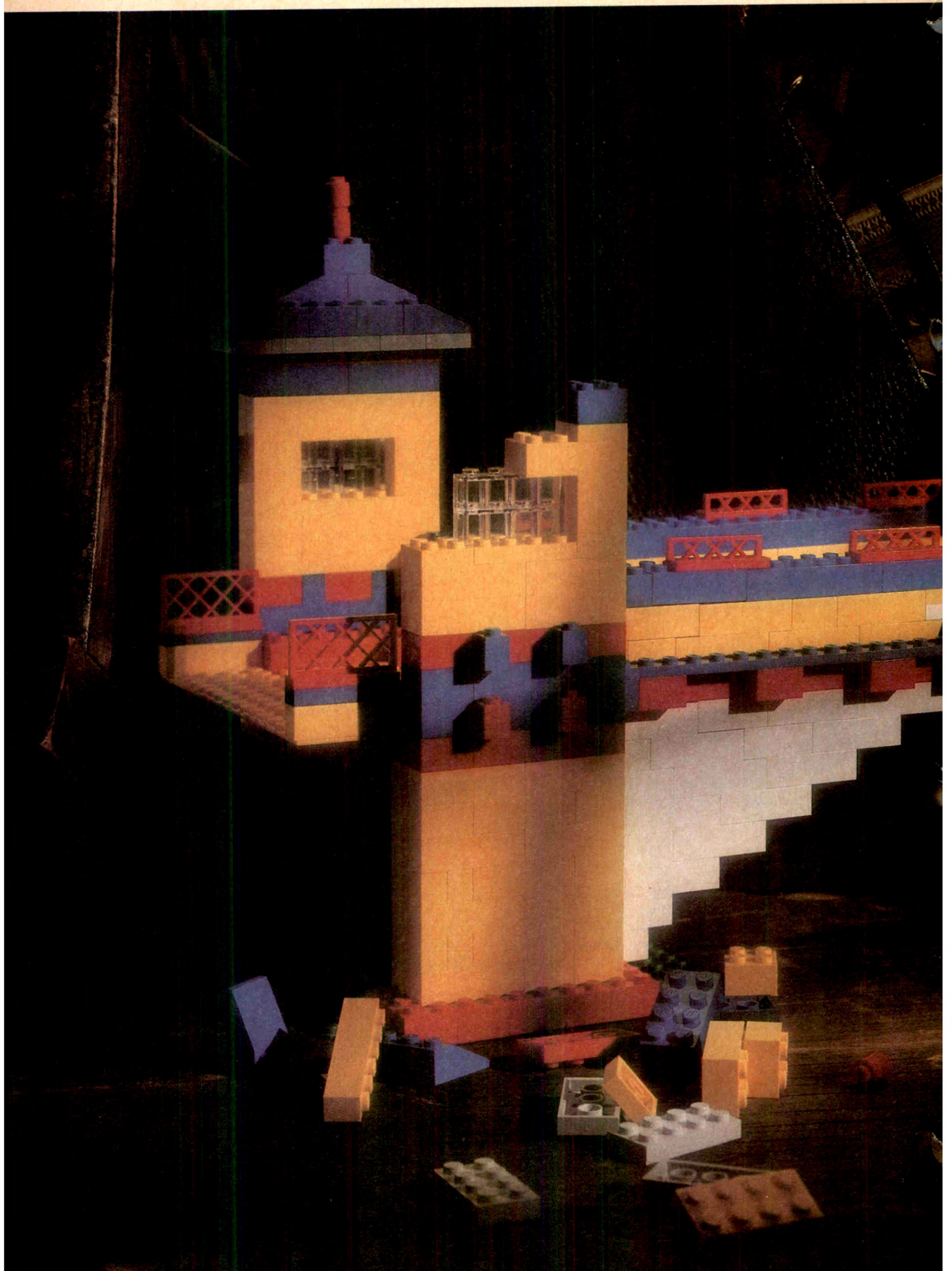
Ventricular Late Potentials and Induced Ventricular Arrhythmias After Surgical Repair of Tetralogy of Fallot

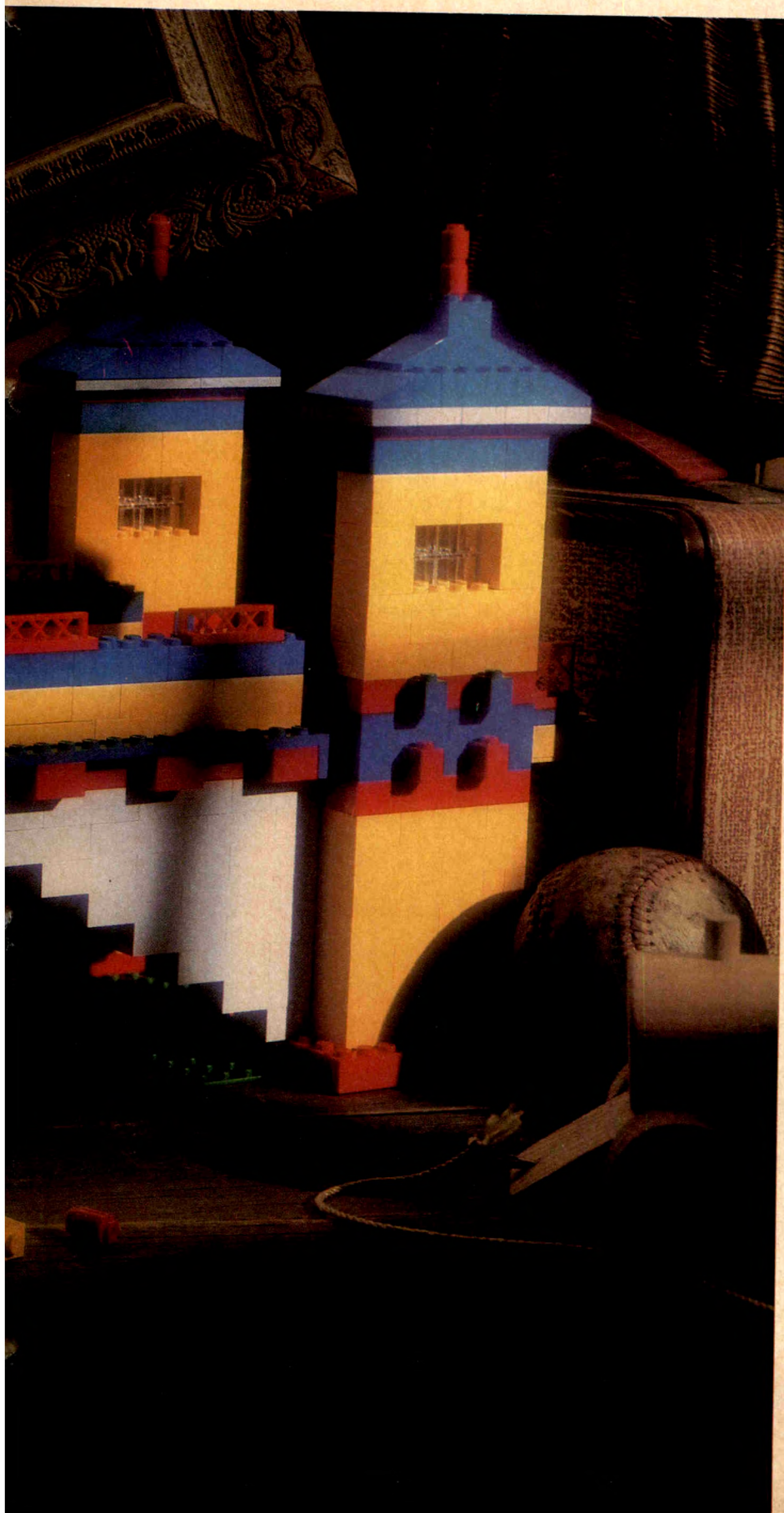
Marc Zimmermann, Beat Friedli, Richard Adamec, and Ingrid Oberhänsli

We prospectively studied 31 asymptomatic patients with postoperative tetralogy of Fallot. Ventricular late potentials were detected in 10 of 31 patients (32%), spontaneous ventricular premature complexes (VPCs) in

Continued on page A34

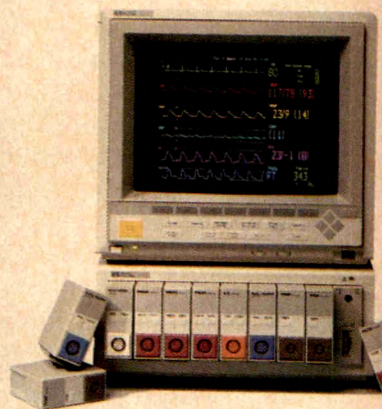
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12 of 31 cases (39%) and nonsustained ventricular tachycardia (VT) was induced in 3 patients (10%). Patients with inducible VT more often had late potentials (3 of 3 vs 7 of 28, $p < 0.01$) and VPCs during Holter monitoring (3 of 3 vs 9 of 28, $p < 0.05$) than did those without them. It is concluded that shortly after repair of tetralogy of Fallot, the presence of both spontaneous VPCs and ventricular late potentials are associated with an increased incidence of inducible VT. Conversely, the absence of VPCs and late potentials may identify patients at low risk of subsequent ventricular arrhythmias.

MISCELLANEOUS

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Thallium-201 Stress Scintigraphy in Takayasu Arteritis

Yuji Hashimoto, Fujio Numano, Yoshiaki Maruyama, Toshiyuki Oniki, Kenji Kasuya, Tsunekazu Kakuta, Tomoko Wada, Michiyoshi Yajima, and Hidenori Maezawa

We studied 38 women with Takayasu arteritis using thallium-201 stress myocardial scintigraphy. Twenty (53%) had abnormal scintigraphic findings (group A). Group A patients had a tendency to be older than group N patients ($n = 18$) and to have a high prevalence of complicated aortic regurgitation. Echocardiographic left ventricular hypertrophy was present in group A. Left ventricular hypertrophy or ischemic ST change on electrocardiography was also frequent in group A. Systemic hypertension was observed in the catheterized group A patients. Coronary ostial stenoses were found in 2 group A patients. The scintigraphic abnormalities were responsible for a decrease in coronary reserve or myocardial damage, or both, due to systemic hypertension or aortic regurgitation.

BRIEF REPORTS

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Usefulness of Dipyridamole-Handgrip Echocardiography Test for Detecting Coronary Artery Disease

Eva Mandysova, Petr Niederle, Anna Malkova, Rudolf Feuereisl, Vaclav Cervenka, Michael Aschermann, and Frantisek Mandys

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Comparison of Manual Versus Automated Edge Detection for Determining Degrees of Luminal Narrowing by Quantitative Coronary Angiography

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Multiple Accessory Pathways in the Wolff-Parkinson-White Syndrome as a Risk Factor for Ventricular Fibrillation

Wee Siong Teo, George J. Klein, Gerard M. Guiraudon, Raymond Yee, James W. Leitch, Douglas McLellan, Richard A. Leather, and You Ho Kim

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Before using Lanoxin Tablets, the physician should be thoroughly familiar with the basic pharmacology of this drug as well as its drug interactions, indications, and usage.

DESCRIPTION: Lanoxin is digoxin, one of the cardiac (or digitalis) glycosides, a closely related group of drugs having in common specific effects on the myocardium.

INDICATIONS AND USAGE:

Heart Failure: The increased cardiac output resulting from the inotropic action of digoxin ameliorates the disturbances characteristic of heart failure (venous congestion, edema, dyspnea, orthopnea and cardiac asthma).

Digoxin is more effective in "low output" (pump) failure than in "high output" heart failure secondary to arteriovenous fistula, anemia, infection or hyperthyroidism.

Digoxin is usually continued after failure is controlled, unless some known precipitating factor is corrected. Studies have shown, however, that even though hemodynamic effects can be demonstrated in almost all patients, corresponding improvement in the signs and symptoms of heart failure is not necessarily apparent. Therefore, in patients in whom digoxin may be difficult to regulate, or in whom the risk of toxicity may be great (e.g., patients with unstable renal function or whose potassium level tends to fluctuate) a cautious withdrawal of digoxin may be considered. If digoxin is discontinued, the patient should be regularly monitored for clinical evidence of recurrent heart failure.

CONTRAINDICATIONS: Digitalis glycosides are contraindicated in ventricular fibrillation.

In a given patient, an untoward effect requiring permanent discontinuation of other digitalis preparations usually constitutes a contraindication to digoxin. Hypersensitivity to digoxin itself is a contraindication to its use. Allergy to digoxin, though rare, does occur. It may not extend to all such preparations, and another digitalis glycoside may be tried with caution.

WARNINGS: Digitalis alone or with other drugs has been used in the treatment of obesity. This use of digoxin or other digitalis glycosides is unwarranted. Moreover, since they may cause potentially fatal arrhythmias or other adverse effects, the use of these drugs solely for the treatment of obesity is dangerous.

Anorexia, nausea, vomiting and arrhythmias may accompany heart failure or may be indications of digitalis intoxication. Clinical evaluation of the cause of these symptoms should be attempted before further digitalis administration. In such circumstances determination of the serum digoxin concentration may be an aid in deciding whether or not digitalis toxicity is likely to be present. If the possibility of digitalis intoxication cannot be excluded, cardiac glycosides should be temporarily withheld, if permitted by the clinical situation.

Patients with renal insufficiency require smaller than usual maintenance doses of digoxin (see DOSAGE AND ADMINISTRATION section).

Heart failure accompanying acute glomerulonephritis requires extreme care in digitalization. Relatively low loading and maintenance doses and concomitant use of antihypertensive drugs may be necessary and careful monitoring is essential. Digoxin should be discontinued as soon as possible.

Patients with severe cardiacitis, such as cardiacitis associated with rheumatic fever or viral myocarditis, are especially sensitive to digoxin-induced disturbances of rhythm.

Newborn infants display considerable variability in their tolerance to digoxin. Premature and immature infants are particularly sensitive, and dosage must not only be reduced but must be individualized according to their degree of maturity. Note: Digitalis glycosides are an important cause of accidental poisoning in children.

PRECAUTIONS:

General: Digoxin toxicity develops more frequently and lasts longer in patients with renal impairment because of the decreased excretion of digoxin. Therefore, it should be anticipated that dosage requirements will be decreased in patients with moderate to severe renal disease (see DOSAGE AND ADMINISTRATION section). Because of the prolonged half-life, a longer period of time is required to achieve an initial or new steady-state concentration in patients with renal impairment than in patients with normal renal function.

In patients with hypokalemia, toxicity may occur despite serum digoxin concentrations within the "normal range," because potassium depletion sensitizes the myocardium to digoxin. Therefore, it is desirable to maintain normal serum potassium levels in patients being treated with digoxin. Hypokalemia may result from diuretic, amphotericin B or corticosteroid therapy, and from dialysis or mechanical suction of gastrointestinal secretions. It may also accompany malnutrition, diarrhea, prolonged vomiting, old age and long-standing heart failure. In general, rapid changes in serum potassium or other electrolytes should be avoided, and intravenous treatment with potassium should be reserved for special circumstances as described below (see TREATMENT OF ARRHYTHMIAS PRODUCED BY OVERDOSEAGE section).

Calcium, particularly when administered rapidly by the intravenous route, may produce serious arrhythmias in digitalized patients. Hypercalcemia from any cause predisposes the patient to digitalis toxicity. On the other hand, hypocalcemia can nullify the effects of digoxin in man; thus, digoxin may be ineffective until serum calcium is restored to normal. These interactions are related to the fact that calcium affects contractility and excitability of the heart in a manner similar to digoxin.

Hypomagnesemia may predispose to digitalis toxicity. If low magnesium levels are detected in a patient on digoxin, replacement therapy should be instituted.

Quinidine, verapamil, and amiodarone cause a rise in serum digoxin concentration, with the implication that digitalis intoxication may result. This rise appears to be proportional to the dose. The effect is mediated by a reduction in the digoxin clearance and, in the case of quinidine, decreased volume of distribution as well.

Certain antibiotics may increase digoxin absorption in patients who convert digoxin to inactive metabolites in the gut (see Pharmacokinetics portion of the CLINICAL PHARMACOLOGY section). Recent studies have shown that specific colonic bacteria in the lower gastrointestinal tract convert digoxin to cardioinactive reduction products, thereby reducing its bioavailability. Although inactivation of these bacteria by antibiotics is rapid, the serum digoxin concentration will rise at a rate consistent with the elimination half-life of digoxin. The magnitude of rise in serum digoxin concentration relates to the extent of bacterial inactivation, and may be as much as two-fold in some cases.

Patients with acute myocardial infarction or severe pulmonary disease may be unusually sensitive to digoxin-induced disturbances of rhythm.

Atrial arrhythmias associated with hypermetabolic states (e.g., hyperthyroidism) are particularly resistant to digoxin treatment. Large doses of digoxin are not recommended as the only treatment of these arrhythmias and care must be taken to avoid toxicity if large doses of digoxin are required. In hypothyroidism, the digoxin requirements are reduced. Digoxin responses in patients with compensated thyroid disease are normal.

Reduction of digoxin dosage may be desirable prior to electrical cardioversion to avoid induction of ventricular arrhythmias, but the physician must consider the consequences of rapid increase in ventricular response to atrial fibrillation if digoxin is withheld to 1 to 2 days prior to cardioversion. If there is a suspicion that digitalis toxicity exists, elective cardioversion should be delayed. If it is not prudent to delay cardioversion, the energy level selected should be minimal at first and carefully increased in an attempt to avoid precipitating ventricular arrhythmias.

Incomplete AV block, especially in patients with Stokes-Adams attacks, may progress to advanced or complete heart block if digoxin is given.

In some patients with sinus node disease (i.e., Sick Sinus Syndrome), digoxin may worsen sinus bradycardia or sinoatrial block.

In patients with Wolff-Parkinson-White Syndrome and atrial fibrillation, digoxin can enhance transmission of impulses through the accessory pathway. This effect may result in extremely rapid ventricular rates and even ventricular fibrillation. Digoxin may worsen the outflow obstruction in patients with idiopathic hypertrophic subaortic stenosis (IHSS). Unless cardiac failure is severe, it is doubtful whether digoxin should be employed.

Patients with chronic constrictive pericarditis may fail to respond to digoxin. In addition, slowing of the heart rate by digoxin in some patients may further decrease cardiac output.

Patients with heart failure from amyloid heart disease or constrictive cardiomyopathies respond poorly to treatment with digoxin.

Digoxin is not indicated for the treatment of sinus tachycardia unless it is associated with heart failure.

Digoxin may produce false positive ST-T changes in the electrocardiogram during exercise testing.

Intramuscular injection of digoxin is extremely painful and offers no advantages unless other routes of administration are contraindicated.

Laboratory Tests: Patients receiving digoxin should have their serum electrolytes and renal function (BUN and/or serum creatinine) assessed periodically; the frequency of assessments will depend on the clinical setting. For discussion of serum digoxin concentrations, see DOSAGE AND ADMINISTRATION section in the complete prescribing information.

Drug Interactions: Potassium-depleting corticosteroids and diuretics may be major contributing factors to digitalis toxicity. Calcium, particularly if administered rapidly by the intravenous route, may produce serious arrhythmias in digitalized patients. Quinidine, verapamil, and amiodarone cause a rise in serum digoxin concentration, with the implication that digitalis intoxication may result. Certain antibiotics increase digoxin absorption in patients who convert digoxin to inactive metabolites in the lower intestine, so that digitalis intoxication may result. Propantheline and diphenoxylate, by decreasing gut motility, may increase digoxin absorption. Antacids, kaolin-pectin, sulfasalazine, neomycin, cholestyramine and certain anticancer drugs may interfere with intestinal digoxin absorption, resulting in unexpectedly low serum concentrations. There have been inconsistent reports regarding the effects of other drugs on the serum digoxin concentration. Thyroid administration to a digitalized, hypothyroid patient may increase the dose requirement of digoxin. Concomitant use of digoxin and sympathomimetics increases the risk of cardiac arrhythmias because both enhance ectopic pacemaker activity. Succinylcholine may cause a sudden extrusion of potassium from muscle cells, and may thereby cause arrhythmias in digitalized patients. Although β adrenergic blockers or calcium channel blockers and digoxin may be useful in combination to control atrial fibrillation, their additive effects on AV node conduction can result in complete heart block.

Due to the considerable variability of these interactions, digoxin dosage should be carefully individualized when patients receive coadministered medications. Furthermore, caution should be exercised when combining digoxin with any drug that may cause a significant deterioration in renal function, since this may impair the excretion of digoxin.

Carcinogenesis, Mutagenesis, Impairment of Fertility: There have been no long-term studies performed in animals to evaluate carcinogenic potential.

Pregnancy: Teratogenic Effects: Pregnancy Category C. Animal reproduction studies have not been conducted with digoxin. It is also not known whether digoxin can cause fetal harm when administered to a pregnant woman or affect reproduction capacity. Digoxin should be given to a pregnant woman only if clearly needed.

Nursing Mothers: Studies have shown that digoxin concentrations in the mother's serum and milk are similar. However, the estimated daily dose to a nursing infant will be far below the usual infant maintenance dose. Therefore, amount should have no pharmacologic effect upon the infant. Nevertheless, caution should be exercised when it is administered to a nursing woman.

ADVERSE REACTIONS: The frequency and severity of adverse reactions to digoxin depend on the dose and on administration, as well as on the patient's underlying disease or concomitant therapies (see PRECAUTIONS and Serum Digoxin Concentrations subsection of DOSAGE AND ADMINISTRATION). The overall incidence of adverse reactions has been reported as 5 to 20%, with 15 to 20% of them being considered serious (one to four percent of patients receiving digoxin). Evidence suggests that the incidence of toxicity has decreased since the introduction of serum digoxin assay and improved standardization of digoxin tablets. Cardiac toxicity accounts for about one-fourth of the adverse reactions, and CNS and other toxicity for about one-fourth of these adverse reactions.

Adults:

Cardiac:—Unifocal or multifocal premature contractions, especially in bigeminal or trigeminal pattern that most common arrhythmias associated with digoxin toxicity in adults with heart disease.

Ventricular tachycardia may result from digitalis toxicity. Atrioventricular (AV) dissociation, accelerated junctional rhythm and atrial tachycardia with block are also common arrhythmias caused by digoxin overdose.

Excessive slowing of the pulse is a clinical sign of digoxin overdose. AV block (Wenckebach) of increasing degree may proceed to complete heart block.

Note: The electrocardiogram is fundamental in determining the presence and nature of these cardiac disturbances. Digoxin may also induce other changes in the ECG (e.g., PR prolongation, ST depression), which represent digitalis effects and may or may not be associated with digitalis toxicity.

Gastrointestinal:—Anorexia, nausea, vomiting and less commonly diarrhea are common early symptoms of overdose. However, uncontrolled heart failure may also produce such symptoms. Digitalis toxicity very rarely may cause abdominal and hemorrhagic necrosis of the intestines.

CNS:—Visual disturbances (blurred or yellow vision), headache, weakness, dizziness, apathy and psychosis can occur.

Other:—Gynecomastia is occasionally observed. Maculopapular rash or other skin reactions are rarely observed.

Infants and Children: Toxicity differs from the adult in a number of respects. Anorexia, nausea, vomiting, diarrhea and CNS disturbances may be present but are rare as initial symptoms in infants. Cardiac arrhythmias are more readily induced in children than in adults. Digoxin in children may produce any arrhythmia. The most commonly encountered are conduction disturbances or supraventricular tachyarrhythmias, such as atrial tachycardia with or without block, and junctional (nodal) tachycardia. Ventricular arrhythmias are less common. Sinus bradycardia may also be a sign of impending digoxin intoxication, especially in infants, even in the absence of first degree heart block. Any arrhythmia or alteration in cardiac conduction that develops in a child taking digoxin should initially be assumed to be a consequence of digoxin intoxication.

OVERDOSEAGE:

Treatment of Arrhythmias Produced by Overdose:

Adults: Digoxin should be discontinued until all signs of toxicity are gone. Discontinuation may be all that is needed if toxic manifestations are not severe and appear only near the expected time for maximum effect of the drug.

Correction of factors that may contribute to toxicity such as electrolyte disturbances, hypoxia, acid-base disturbances and removal of aggravating agents such as catecholamines, should also be considered. Potassium salts may be indicated, particularly if hypokalemia is present. Potassium administration may be dangerous in the setting of massive digitalis overdose (see Massive Digitalis Overdose subsection below). Potassium chloride in divided oral doses totaling 3 to 6 grams of the salt (40 to 80 mEq K+) for adults may be given provided renal function is adequate below for potassium recommendations in Infants and Children).

When correction of the arrhythmia is urgent and the serum potassium concentration is low or normal, potassium should be administered intravenously in 5% dextrose injection. For adults, a total of 40 to 80 mEq (diluted to a concentration of 40 mEq per 500 mL) may be given at a rate not exceeding 20 mEq per hour, or slower if limited by pain due to irritation. Additional amounts may be given if the arrhythmia is uncontrolled and potassium well-tolerated. ECG monitoring should be performed to watch for any evidence of potassium toxicity (e.g., peaking of T waves) and to observe the effect on the arrhythmia. The infusion may be stopped when the desired effect is achieved.

Note: Potassium should not be used and may be dangerous in heart block due to digoxin, unless primarily related to supraventricular tachycardia.

Other agents that have been used for the treatment of digoxin intoxication include lidocaine, procainamide, propranolol and phenytoin, although use of the latter must be considered experimental. In advanced heart block, atropine and temporary ventricular pacing may be beneficial. Digibind® (Digoxin Immune Fab) (Ovine), can be used to reverse potent life-threatening digoxin (or digitoxin) intoxication. Improvement in signs and symptoms of digitalis toxicity usually begins within 1/2 hour of Digibind administration. Each 40 mg vial of Digibind will neutralize 0.6 mg of digoxin (which is a usual body dose of an adequately digitalized 70 kg patient).

Infants and Children: See Adult section for general recommendations for the treatment of arrhythmias produced by overdose and for cautions regarding the use of potassium.

If a potassium preparation is used to treat toxicity, it may be given orally in divided doses totaling 1 to 1.5 mEq per kilogram (kg) body weight (1 gram of potassium chloride contains 13.4 mEq K+).

When correction of the arrhythmia with potassium is urgent, approximately 0.5 mEq/kg of potassium per hour may be given intravenously, with careful ECG monitoring. The intravenous solution of potassium should be diluted enough to avoid local irritation; however, especially in infants, care must be taken to avoid intravenous fluid overload.

DOSAGE AND ADMINISTRATION: Recommended dosages are average values that may require considerable modification because of individual sensitivity or associated conditions. Diminished renal function is the most important factor requiring modification of recommended doses.

- In deciding the dose of digoxin, several factors must be considered:
 - The disease being treated. Atrial arrhythmias may require larger doses than heart failure.
 - The body weight of the patient. Doses should be calculated based upon lean or ideal body weight.
 - The patient's renal function, preferably evaluated on the basis of creatinine clearance.
 - Age is an important factor in infants and children.
 - Concomitant disease states, drugs or other factors likely to alter the expected clinical response to digoxin (see PRECAUTIONS and Drug Interactions sections).

Consult complete product information before prescribing.

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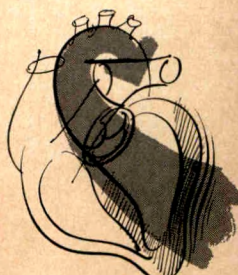
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An Economic Evaluation of Lovastatin for Cholesterol Lowering and Coronary Artery Disease Reduction

Joel W. Hay, PhD, Ellison H. Wittels, MD, and Antonio M. Gotto, Jr., MD, DPhil

The costs and benefits of cholesterol lowering in the primary prevention of coronary artery disease (CAD) were considered using lifetime lovastatin therapy as the intervention model for adults between 35 and 55 years of age. The analysis projected the benefits of CAD risk reduction using estimates from the Framingham Heart Study. The chosen analytic perspective was that of the patient.

For average-risk men with total serum cholesterol levels between 5.69 and 9.83 mmol/liter (220 and 380 mg/dl), the cost per life-year saved ranged from \$9,000 to \$106,000, whereas for average-risk women, the cost ranged from \$35,000 to \$297,000 (1989 U.S. dollars). In high-risk men (with smoking habit and hypertension), the cost per life-year saved values ranged from \$6,000 to \$53,000, whereas in high-risk women the cost per life-year saved values ranged from \$19,000 to \$160,000.

The results were more favorable than those found in previous studies of alternate medication therapies for hypercholesterolemia. Even using conservative parameter assumptions, at least 800,000 Americans aged 35 to 55 years are at sufficiently high risk for CAD, so that the net

cost of lovastatin therapy can be favorably compared with other widely used medical interventions.

(Am J Cardiol 1991;67:789-796)

Total serum cholesterol and its low-density lipoprotein components have been identified as important risk factors in coronary artery disease (CAD).^{1,2} A 1985 National Institutes of Health consensus conference reported that those with cholesterol levels ≥ 6.21 mmol/liter (240 mg/dl) (about 30% of the adult U.S. population) are at increased risk of premature CAD.³ A recent consensus panel update concluded that in addition to those with cholesterol >6.21 mmol/liter (240 mg/dl), persons with cholesterol levels between 5.17 and 6.21 mmol/liter (200 and 240 mg/dl) with added CAD risk factors should also consider cholesterol reduction strategies.⁴ Analysis of death reports in roughly 365,000 men initially screened for the Multiple Risk Factor Intervention Trial showed that the increasing relation between cholesterol and age-adjusted CAD death rates is continuous and graded.¹ Several studies, notably the Lipid Research Clinics Coronary Primary Prevention Trial and the Helsinki Heart Study, showed that cholesterol modification will prevent CAD.⁵⁻⁷

Better understanding of the cost-effectiveness of cholesterol reduction will assist physicians, health policymakers and patients in decisions regarding the allocation of resources toward cholesterol screening, monitoring and preventive intervention. Thus far, the published evidence on the potential economic benefits has not been highly favorable.⁸⁻¹² Currently, applicable methods and data for economic analysis of heart disease prevention strategies are not ideal. However, in dealing with an issue as important as the allocation of scarce

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The views expressed here are solely those of the authors. A technical appendix containing additional data and methodologic details is available on written request to Dr. Hay, The Hoover Institution, Stanford, California, 94305-6010.

TABLE I Framingham Study Risk of Coronary Artery Disease by Age, Sex, Cholesterol (Five-Year Risk)

Serum Cholesterol— mmol/liter (mg/dl)	Age 35 Years				Age 55 Years			
	Women (%)		Men (%)		Women (%)		Men (%)	
	Non-Smoker	Smoker	Non-Smoker	Smoker	Non-Smoker	Smoker	Non-Smoker	Smoker
5.69 (220)	0.4	0.4	1.0	1.5	2.7	2.9	5.5	7.9
7.76 (300)	0.7	0.7	2.7	3.9	3.8	4.1	8.8	12.3
9.83 (380)	1.1	1.2	6.7	9.6	5.4	5.9	13.6	18.4
Additional risk assumptions								
Systolic Blood Pressure 133				Abnormal ECG 1%		Glucose Intolerance 6%		
Cholesterol measurements are converted at 1 mg/dl = 0.02586 mmol/liter. Adapted from Abbot et al. ¹⁸ ECG = electrocardiogram.								

public and private resources to prevention of CAD, there is no satisfactory alternative to reasoned cost-effectiveness arguments based on the best available data. The recent U.S. Food and Drug Administration marketing approval for lovastatin, a hydroxymethylglutaryl coenzyme A reductase inhibitor, has met with substantial interest. Lovastatin has been found to be effective in reducing low-density and increasing high-density cholesterol in patients with familial and nonfamilial hypercholesterolemia.^{13,14} Although prospective studies investigating a causal reduction in CAD-related illnesses resulting from lovastatin intervention are not yet completed, the evidence from retrospective studies and prospective clinical trials of other lipid medications suggests that the clinical benefits of lovastatin therapy may be substantial.^{1,2,5-7} This study examines the economic issues of CAD prevention through cholesterol reduction, in the context of what is currently known about the clinical, economic and safety profiles for lovastatin.

METHODS

Our chosen measure of the costs and benefits of cholesterol lowering, presented from the perspective of the individual patient, is the present expected value of the cost per life-year saved.¹⁵ Reduction in CAD will lead to savings in indirect costs, consisting of the value of time gained due to reduced morbidity, disability and mortality. With cost per life-year saved modeling, rather than placing explicit monetary value on this expected time gain, benefits are measured in terms of the average life expectancy increases resulting from intervention. For a given reduction in cholesterol, the net costs of intervention are standardized by the life expectancy gains. In this context, the net costs consist of the intervention plus side effect costs, minus the reductions in expected medical costs, since cholesterol lowering decreases CAD.

We estimated the CAD incidence from the Framingham Study multivariate logistic risk equa-

tions.¹⁶⁻¹⁹ Comparisons of the Framingham CAD risk estimates with those from a variety of other epidemiologic studies indicate a high degree of conformity.^{10,19}

CAD risk increases with age and cholesterol level for both sexes, reaching >2% per year for many men and women by age 55. Table I shows the Framingham Study estimated 5-year risk of CAD for smoking and nonsmoking adults at specified cholesterol levels, 2 age groups and both sexes. Other model primary risk factors (systolic blood pressure, diabetes, left ventricular hypertrophy by electrocardiogram) were set at population averages.

Evidence on the relation between cholesterol-lowering interventions and the achievable reduction in CAD events is from a small number of prospective randomized clinical trials. The most prominent of these, the Lipid Research Clinics Trial, showed a 19% reduction in combined fatal and nonfatal CAD associated with a 9 to 11% decrease in cholesterol.^{3,6} These studies were used to develop the National Institutes of Health consensus rule of thumb that "... each 1% reduction in blood cholesterol level yields approximately a 2% reduction in CAD rates."³ The results presented here are based on Framingham risk equation predictions. Our results based on the more optimistic 1%:2% rule are available on request.

We projected the effects of cholesterol levels on CAD risk and expected disease costs for different age intervals (35 to 55 years of age), 5 cholesterol levels (5.69 to 9.83 mmol/liter; 220 to 380 mg/dl) and both sexes. Unlike Berwick¹⁰ or Taylor¹² and their co-workers in projecting disease risk, we made no attempt to adjust for individual variation in repeated cholesterol readings, since the Framingham equations we used were estimated with data from single-reading observed cholesterol levels. This would tend to bias our benefits estimates downward.

The model conservatively ignored reduction in secondary CAD due to cholesterol lowering. Recent Fra-

mingham Study estimates of the reduction in secondary CAD events associated with a given percentage of cholesterol reduction²⁰ did not provide sufficient precision for adjusting our disease risk estimates. Following previous researchers,¹⁰ we assumed that a person who reduces his or her cholesterol level from $(i + x)$ to i would have a corresponding reduction in CAD risk to not less than that of a person starting at cholesterol level i , based on Framingham probability estimates. We assumed the level of achievable benefits to be a fraction, F , of these maximum benefits. Lacking contrary evidence, F was assumed to range from 70 to 100%, with a baseline level of 90%.

The value of a cholesterol-lowering intervention is influenced by the magnitude of cholesterol reduction that can be achieved and the time lag before the benefits of lower serum cholesterol levels are achieved.^{6,8,10} Lovastatin, 20 mg once per evening, produces an average 18 to 22% reduction in cholesterol, whereas 20 mg twice daily produces an average 28 to 30% reduction in cholesterol.¹³ These figures may understate the intervention benefits, since the effects of lovastatin therapy on high- and low-density lipid levels are better than would be reflected in an intervention (e.g., dietary intervention) that lowered all cholesterol lipid components by an equal percentage.¹³ Consistent with the findings of the Lipid Research Clinics Trial and the Helsinki Heart Study, we included a time lag, L , before benefits of a cholesterol-reducing intervention are observed.⁵⁻⁷ Initially, this lag was assumed to be 2 years, with a range of 0 to 4 years. Conservatively, no benefits from intervention were modeled for the initial period up to L .

Cholesterol levels tend to increase with age in a range that averages roughly 0.03 mmol/liter (1 mg/dl)/year for both men and women. Using Framingham Study equations, any therapeutic intervention that lowers cholesterol by a fixed percentage would be more beneficial assuming a positive cholesterol-age trend than assuming a fixed lifetime cholesterol level in the absence of treatment. However, since the long-term effects of lovastatin on cholesterol levels are not yet known, we conservatively ignored the empirical upward drift in cholesterol with age.

Lovastatin is available in 20-mg tablets costing \$1.25 per tablet. Pharmacy preparation markup averages <30%, and is computed as $(\text{retail price} - \text{cost})/(\text{retail price})$.²¹ Liver function and ophthalmologic examinations are required at baseline and periodically thereafter. An informal survey of physician practices suggests that these additional monitoring tests would add about \$0.64/day to the 5-year therapy costs of lovastatin medication. To account for pharmacy costs, physician costs and other patient costs, we conservative-

ly added \$1.18/day to the average daily cost for lovastatin, making our therapy cost estimate \$2.43/day for 20 mg once each evening (the recommended starting dosage). Because the marketing patent for lovastatin expires in 1997, our use of this therapy cost estimate will likely lead to an overstatement of lifetime treatment costs. Experience with major multisource drugs suggests that generic lovastatin may be available at costs 2 to 10 times lower than the price for the brand name compound.

Although serious side effects associated with lovastatin usage are rare, cases of myositis and rhabdomyolysis have been reported. Rare side effects may be uncovered when a drug proceeds beyond the clinical trial phase to widescale use. However, experience with approximately 1 million patients since marketing approval suggests that the incidence of adverse effects thus far has been extremely low.²² Even if some such side effects were later found to be associated with lovastatin use, they would probably not add substantially to the total cost of therapy. For example, a hypothetical 1/10,000 adverse effect or complication costing \$200,000 to treat would add an average \$20 to the lifetime patient-therapy costs. (Long-term side effects are discussed later.)

Life expectancy and age- and sex-specific probabilities of mortality from causes other than CAD were taken from U.S. vital statistics.^{23,24} We used Framingham Study data on the reduction in survival years of life after an initial occurrence of myocardial infarction and angina pectoris to adjust the age- and sex-specific life expectancies for the premature death of patients with CAD not dying during the first episode of CAD.^{20,25,26}

We used national data²⁷ on the reported annual increase in bed disability days for patients with CAD relative to the general population to adjust life expectancy for nonfatal CAD at each age level under the assumption that bed disability days were equivalent to 75% of healthy days. As shown below, the results are seldom changed if bed disability days are assumed to be equivalent to any fraction (0 to 100%) of healthy days. The base case annual discount rate used in the analysis was 5%, with a range of 3 to 7%.¹⁰

Medical costs for treating specific CAD diagnoses have risen substantially over the past 20 years. No comprehensive national database exists that would allow calculation of the average cost of medical treatment for each type of CAD outcome. We opted to calculate average costs of medical care by developing an expert consensus of patient prognosis, outcome and medical resource use for each of the initial diagnostic events defined in the Framingham Study.²⁸ The medical decision model was based on clinical expert judgment regarding appropriate state-of-the-art treatment, as

practiced in advanced CAD treatment and research facilities. As shown below, the level of medical costs has a relatively small effect on cost per life-year saved estimates.

RESULTS

The base case model results are presented in Table II for average levels of Framingham equation risk factors other than cholesterol. The analysis is based on an intervention of lovastatin, 20 mg/day, up to age 75. It was assumed that this intervention would achieve an

average of 20% reduction in cholesterol levels, at an annual cost of \$886.

The effects of cholesterol lowering on CAD risk is greatly impacted by the level of other disease risk factors besides age, sex and initial cholesterol level. The Framingham Study equations implied a multiplicative rather than an additive relation. Table III gives cost per life-year saved values for the same intervention (lovastatin 20 mg/day) in high-risk adults. These persons were assumed to have systolic blood pressures of 180 mm Hg. They were assumed to be at an average risk

TABLE II Baseline Case Cost Per Life-Year Saved: By Age, Cholesterol (\$1,000s)

Serum Cholesterol— mmol/liter (mg/dl)	Age 35 Years				Age 55 Years			
	Women		Men		Women		Men	
	Non-Smoker	Smoker	Non-Smoker	Smoker	Non-Smoker	Smoker	Non-Smoker	Smoker
5.69–4.55 (220–176)	\$297	\$225	\$86	\$57	\$278	\$204	\$106	\$68
6.72–5.38 (260–208)	\$167	\$126	\$53	\$36	\$154	\$112	\$75	\$48
7.76–6.21 (300–240)	\$108	\$82	\$34	\$23	\$111	\$80	\$54	\$35
8.79–7.03 (340–272)	\$70	\$54	\$21	\$14	\$81	\$58	\$40	\$25
9.83–7.86 (380–304)	\$46	\$35	\$13	\$9	\$59	\$43	\$29	\$19
Additional model assumptions								
20% Cholesterol Reduction with Two Years Required to Achieve Benefits								
Prevention Costs/Year \$886	Discount Rate 5.0%		Systolic Blood Pressure 133 mm Hg		Abnormal ECG 1%		Glucose Intolerance 6%	

ECG = electrocardiogram.

TABLE III High-Risk Case Cost Per Life-Year Saved: By Age, Cholesterol (\$1,000s)

Serum Cholesterol— mmol/liter (mg/dl)	Age 35 Years				Age 55 Years			
	Women		Men		Women		Men	
	Non-Smoker	Smoker	Non-Smoker	Smoker	Non-Smoker	Smoker	Non-Smoker	Smoker
5.69–4.55 (220–176)	\$160	\$120	\$46	\$31	\$151	\$110	\$53	\$34
6.72–5.38 (260–208)	\$89	\$66	\$29	\$20	\$81	\$58	\$38	\$25
7.76–6.21 (300–240)	\$57	\$43	\$19	\$13	\$58	\$41	\$27	\$18
8.79–7.03 (340–272)	\$37	\$28	\$12	\$9	\$42	\$30	\$20	\$14
9.83–7.86 (380–304)	\$24	\$19	\$8	\$6	\$31	\$22	\$15	\$11
Additional model assumptions								
20% Cholesterol Reduction with Two Years Required to Achieve Benefits								
Prevention Costs/Year \$886	Discount Rate 5.0%		Systolic Blood Pressure 180 mm Hg		Abnormal ECG 1%		Glucose Intolerance 6%	

ECG = electrocardiogram.

for diabetes and left ventricular hypertrophy seen on the electrocardiogram. Although not shown in the table, the addition of diabetes as a CAD risk factor in women with high blood pressure and smoking habits reduced cost per life-year saved values to <\$26,000 for cholesterol levels >6.72 mmol/liter (260 mg/dl). Women with multiple heart disease risks lost much of their female risk advantage.

Tables II and III suggested a simple initial cholesterol screening strategy. Those with ≥ 3 CAD risk factors (male sex, high blood pressure, smoking habit, left ventricular hypertrophy seen on the electrocardiogram or diabetes) would have cost per life-year saved values <\$30,000 for the base case cholesterol-reducing intervention, even with moderately elevated (6.72 mmol/liter; 260 mg/dl) cholesterol. Under our assumptions, it would be cost-effective to intervene in these high-risk subgroups relative to other patients.

Savings in direct medical costs: As is apparent from the positive cost per life-year saved values in Table III, even for high-risk men the base case cholesterol-reducing intervention would not reduce the expected amount of restorative CAD medical treatment enough to lower average total net medical costs. Thus, from a narrow health care expenditure perspective, lovastatin therapy would be considered as "cost-enhancing" rather than "cost-reducing." Nevertheless, the cost of saving a year of life with lovastatin therapy for high-risk patients would compare favorably with a broad spectrum of other medical interventions (see Figure 1).²⁹ Lovastatin was also cost-effective relative to cholestyramine or colestipol, since it achieved more than double the average reduction in cholesterol at a similar cost in therapy.^{8,9,11}

Model sensitivity analysis: Table IV summarizes the effects of changing parameter values on the calculated net benefits of cholesterol intervention. Overall, this sensitivity analysis shows the base case results to be quite stable. Large changes in key parameters have less

effect on model results than, e.g., the differences between base case male and female results.

Changes in the assumed level of cholesterol reduction that can be achieved have substantial impact on cost per life-year saved values. Lovastatin and other cholesterol reduction interventions have widely varying efficacies among subjects. Because of the sensitivity of the cost per life-year saved results to the assumed intervention efficacy, these variations would lead to substantial variance in projected CAD risk reduction and estimated cost per life-year saved values among persons. As expected, changes in the ratio of CAD patient survival relative to average survival led to about a one-for-one percent change in cost per life-year saved values.

Changes in the daily therapy costs led to slightly less than one-for-one percent changes in cost per life-year saved values. Table IV suggests that the assumed level of CAD medical care costs would not have a major impact on model calculations. If medical care costs were either doubled or were zero, the cost per life-year saved values would only change by $\leq 20\%$. This highlights the finding that most of the benefits of reducing CAD risk were related to increased life expectancy rather than reduced medical costs. The percentage used to weigh patient bed disability days in relation to healthy days had little impact on results.

Another issue we considered was the potential adverse effects from long-term usage of lovastatin. It is not possible to extrapolate the long-term effects of lovastatin on, e.g., liver or kidney function. However, for the sake of argument, suppose that each patient undergoing long-term lovastatin therapy had a 20% chance of major health problems after 30 years, resulting from long-term medication side effects, and that these health problems would then cost an average \$100,000 to treat. Using our base case discount rate of 5%, this scenario would have about the same effect on results as adding \$1/day to therapy costs.

FIGURE 1. Medical intervention cost-effectiveness: cost per life-year comparisons. Int. = intensive; mod. = moderate.

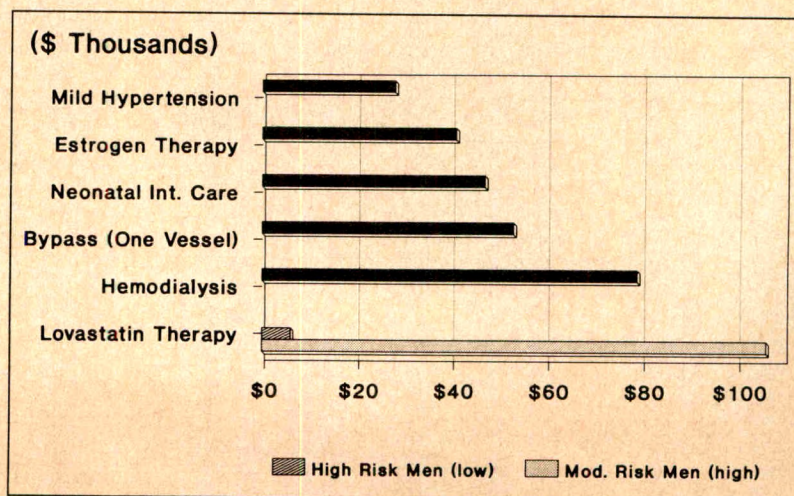


TABLE IV Summary of Model Sensitivity Analysis*

Parameters	Baseline Value	Change Value	Women	Men
Model baseline			\$100	\$30
Discount rate	5%	3%	\$81	\$26
		7%	\$122	\$35
Fraction of maximal potential benefits	90%	100%	\$90	\$28
		70%	\$128	\$38
Years to achieve benefits	2 years	0 years	\$95	\$28
		4 years	\$105	\$34
Cholesterol reduction	20%	30%	\$73	\$20
		10%	\$179	\$58
Acute medical care costs	100%	200%	\$96	\$25
		0%	\$104	\$36
Therapy intervention costs per day	\$2.43	\$1.22	\$48	\$13
		\$3.72	\$155	\$49
Index of survival after initial heart disease event	100%	90%	\$93	\$27
		110%	\$110	\$34
Therapy compliance	100%	80%	\$82	\$24
Bed disability (% of healthy days)	75%	0%	\$98	\$30 [†]
		100%	\$100	\$30 [†]

* Costs per life-year saved (\$1000s) for cholesterol intervention: Age 35, cholesterol 7.76 mmol/liter (300 mg/dl). Other coronary artery disease risk factors are set at U.S. population average levels.

[†] Difference with the baseline was less than rounding to the nearest \$1,000.

Drug therapy compliance: An unknown factor in modeling the benefits of a new drug therapy is the achievable level of therapy compliance. Small to moderate deviations from full compliance would not have adverse impacts on cost per life-year saved values (Table IV), because although small lovastatin dose reductions due to noncompliance have less than a one-for-one impact on the percentage of cholesterol reduction achieved, noncompliance would cause a one-for-one reduction in medication costs, since tablets not taken would be available for future use.

Comparison with fatality risk reduction with seat belt use: Resources allocated to prevention of CAD are scarce and must compete with resources allocated to other social goals. To put the CAD risk reduction potential in a different context, we compared the 5-year mortality risk reduction achievable with a 20% chole-

sterol reduction to the potential maximum mortality risk reduction achievable through mandatory seat belt use. Like CAD, motor vehicle trauma is a major source of preventable mortality and disability across all age and sex cohorts. In the U.S. it is also a leading cause of years of potential life lost.³⁰ Although the actual compliance cost is unknown, achieving full population seat belt usage compliance is far from without cost. Only 33% of U.S. drivers were recently observed to use seat belts, despite mandatory seat belt laws in 29 states.³¹

Table V lists the 5-year mortality risk-reduction benefits of a 20% cholesterol-reducing intervention for adult men and women as multiples of the mortality risk reduction achievable from compulsory seat belt use at various age and cholesterol levels, holding CAD risk factors other than cholesterol at average levels.³² For both men and women, the relative benefits of this intervention ranged from about equal to the benefits of mandatory seat belt use at the lower age and cholesterol levels to 25 to 74 times greater at the higher age and cholesterol levels.

DISCUSSION

In contrast to previous findings in published reports, we concluded that current cholesterol medication could be economically justified, particularly for persons with high levels of primary CAD risk factors. About 8 million U.S. men (35%) aged 35 to 55 years have cholesterol levels ≥ 6.21 mmol/liter (240 mg/dl).³³ Under the conservative assumption that in this cohort the prevalence of cigarette smoking habit (39%)³³ and hypertension (25% of U.S. males aged 35 to 55 years with systolic blood pressure >140 mm Hg)³⁴ are independent of the cholesterol distribution, $\geq 800,000$ U.S. men aged 35 to 55 are at sufficiently high risk for CAD, so that the net cost of drug therapy would be $< \$35,000$ /year of life saved. For women, because the incidence of CAD is lower up to age 55, the benefits of intervention

TABLE V Five-Year Mortality Risk Reduction from a 20% Cholesterol-Lowering Intervention Relative to Mandatory Seat Belt Usage: By Age, Sex and Cholesterol Levels

Serum Cholesterol—mmol/liter (mg/dl)	Age 35 Years				Age 55 Years			
	Women		Men		Women		Men	
	Non-Smoker	Smoker	Non-Smoker	Smoker	Non-Smoker	Smoker	Non-Smoker	Smoker
5.69–4.55 (220–176)	0.9	1.4	0.8	2.5	3.8	5.4	5.6	22.2
7.76–6.21 (300–240)	4.5	6.6	2.5	6.8	9.7	13.9	12.6	41.2
9.83–7.86 (380–304)	19.6	28.2	7.4	17.9	23.1	33.0	25.8	74.3

Index of death risk reduction from mandatory seat belt use = 1.0 for each age and sex category. Adapted from References 18, 31 and 32.

are not as great. Nevertheless, there are a large number of high-risk persons in the U.S. for whom the net cost of cholesterol reduction could be favorably compared to either losses in expected wage earnings or to other widely used medical interventions.

We have avoided presenting estimates of the economic benefits for older adults (aged ≥ 56 years). This is not because there are no benefits from cholesterol reduction in an older population, but because recent investigations suggest that the ratio of total to high-density cholesterol may be more important as a risk factor in older persons than is the cholesterol level by itself.³⁵ CAD risk equations incorporating high-density lipid fractions were not available for our research. If high-density lipid levels are important in adjusting CAD risk in the elderly, then given the high incidence of CAD in this age group, the clinical and economic benefits of a therapeutic intervention such as lovastatin, which both lowers cholesterol and raises high-density lipid fractions, could be substantial.

We opted to use modeling assumptions that provide lower estimates of the benefits of cholesterol reduction than would result from other equally justifiable modeling assumptions. For example, we used the Framingham Study rather than the often cited "1%:2% rule" to provide estimates of CAD lowering through cholesterol reduction.³ We used Framingham cholesterol risk coefficients based on single-reading cholesterol measurements, even though these may substantially underestimate the true risk. We ignored the beneficial effects of lovastatin therapy on high- and low-density lipid fractions and considered only its effects on total serum cholesterol. We conservatively ignored the empirical upward drift in cholesterol level as subjects age.

We use a 5% rate of economic time discount despite the fact that the historical inflation-adjusted rate of interest is closer to 2% in the U.S. and many other countries. We measured savings for avoided medical care due to decreased CAD risk only for 5 years after disease onset. We did not assume that cholesterol lowering has any benefits on secondary disease after CAD onset. Moreover, we assumed that cholesterol lowering produces no decrease in CAD risk for a period of 2 years from initiation of therapy. Finally, because of lack of data and broadly acceptable methods, we ignored the important potential improvements in quality of life resulting from reduction in CAD incidence.

Better information on the outcome efficacy of lovastatin and other cholesterol reduction interventions is needed to establish firm guidelines for efficient allocation of health care resources in reducing CAD risk. To show significant all-cause mortality differences in prospective intervention trials, future studies may require

sample sizes and research costs that are an order of magnitude larger than those of previous clinical trials. Our analysis raises the possibility that broader cholesterol intervention strategies may be cost-effective. For example, it might be appropriate to consider cholesterol lowering in patients with moderately elevated cholesterol, but with refractory smoking habits. Given the substantial social and economic burdens CAD imposes on society, further prospective research into the outcome efficacy of hypercholesterolemia medication is crucial to development of informed CAD prevention policy, and would be justified despite the high research cost.

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Effects of Time Required for Reperfusion (Thrombolysis or Angioplasty, or Both) and Location of Acute Myocardial Infarction on Left Ventricular Functional Reserve Capacity Several Months Later

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The purpose of this study was to determine whether reperfusion of acute myocardial infarction (AMI) by recombinant tissue-type plasminogen activator (rt-PA) or percutaneous transluminal coronary angioplasty, or both, would improve left ventricular (LV) function when it is measured several months later at rest or maximal bicycle exercise, or both. Radionuclide angiography was performed in 44 patients 5 months (range 6 weeks to 9 months) after AMI to assess function, and tomographic myocardial thallium-201 imaging was performed at maximal exercise and delayed rest to determine whether there was any evidence of myocardial ischemia. As expected, no patient had chest pain or redistribution of a thallium defect during the exercise test, because patients had undergone angioplasty (n = 28) or coronary bypass graft surgery (n = 5) where clinically indicated for revascularization. The LV ejection fraction was plotted as a function of the time elapsed between the onset of chest pain and the time when coronary angiography confirmed patency of the infarct-related artery (achieved in 91% of 44 patients by rt-PA [n = 31] or percutaneous transluminal coronary angioplasty [n = 9]). Functional responses differed markedly between patients with anterior (n = 20) versus inferior (n = 24) wall AMI. LV ejec-

tion fraction during exercise correlated with time to reperfusion in patients with an anterior wall AMI ($r = -0.58$; standard error of the estimate = 11.9%; $p < 0.02$) but not in patients with an inferior AMI ($r = 0.10$; standard error of the estimate = 13.1%; difference not significant). LV ejection fraction was higher in patients with an anterior AMI reperfused early (≤ 4.5 hours, $n = 8$) versus late (> 4.5 hours or not at all, $n = 12$) at rest (44 ± 8 vs $32 \pm 9\%$, $p < 0.004$) and exercise (53 ± 9 vs $33 \pm 11\%$, $p < 0.0005$). In contrast, the ejection fraction of patients with an inferior wall AMI ($n = 24$) was not different from that of patients reperfused early ($n = 17$) versus late or not at all ($n = 7$), at rest (42 ± 8 vs $46 \pm 12\%$; difference not significant) or exercise (46 ± 12 vs 55 ± 12 ; difference not significant). It is thus concluded that global LV function and functional reserve during exercise were both improved by reperfusion early (< 4.5 hours) in patients with an anterior wall AMI, but not in patients with an inferior wall AMI. Preservation of LV function during exercise was related to how early reperfusion was achieved in patients with anterior but not inferior wall AMI.

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Therapy for acute myocardial infarction (AMI) by coronary reperfusion is an evolving strategy that seeks to limit infarct size and preserve myocardial function.¹ A reduction in mortality by reperfusion therapy is now well established,²⁻⁴ although this benefit has been conferred primarily on patients with an anterior wall AMI in most studies.² It has been suggested that preservation of left ventricular (LV) function after AMI may improve long-term prognosis

TABLE I Results of Study

	Anterior Wall MI		Inferior Wall MI	
	Early	Late	Early	Late
Patient data				
No. of pts.	8	12	17	7
M:F	8:0	10:2	13:4	1:0
Mean age (yr)	50	54	53	53
Systemic hypertension	5	1	3	6
Heart failure	0	0	0	0
Prior infarct	0	2	2	1
Proximal occlusion*	5	7	12	4
Collateral vessels	2	2	4/13	2/5
Medications				
β blockers	4	3	5	1
Calcium blockers	5	7	9	2
β /calcium blockers	6	10	12	3
Vasodilator	0	1	1	0
Antiarrhythmic	0	0	2	1
Digoxin	0	2	0	1
Exercise SPECT thallium-201				
Time reperfused (hours)	<4.5	≥ 4.5	<4.5	≥ 4.5
Number	8	12	17	7
Exercise test data				
Max heart rate (min^{-1})	132	138	130	132
Max blood pressure (mm Hg)	172	174	160	156
Rate \times pressure (mm Hg/min)	23,000	25,000	21,000	21,000
Angina on exercise test	0	0	0	0
ECG (≥ 0.1 mV ST flat depression)	2	1	1	1
Thallium redistribution	0	0	0	0

* Proximal to first septal perforator in anterior infarct or proximal to posterior descending artery or largest obtuse marginal in inferior infarct.
ECG = electrocardiogram; Max = maximal; MI = myocardial infarction; SPECT = single photon emission computed tomography.

even if there is no demonstrable improvement in short-term prognosis.⁵ This improvement may arise because future infarcts would occur in the setting of better LV function; the final, improved ejection fraction would result in an improved prognosis.⁶⁻⁸

Early studies of LV function after coronary reperfusion by thrombolytic agents yielded conflicting results.⁹⁻¹² The need for intracoronary as opposed to intravenous administration of a thrombolytic agent in these studies delayed reperfusion and reemphasized the importance of early reperfusion.¹³ Recent studies using intravenously administered streptokinase and recombinant tissue-type plasminogen activator (rt-PA) have begun to demonstrate improved LV function.^{14,15} This benefit has been most apparent in patients with an anterior wall AMI, with variable results in patients with an inferior wall AMI.¹⁶ Because small changes in regional LV function may be compensated for by hyperkinesia in noninfarcted segments early after AMI,¹⁷⁻¹⁹ the LV ejection fraction at rest may be a relatively insensitive means of evaluating the preservation of LV function by reperfusion early after AMI. An evaluation of LV function months after AMI, during exercise, should provide a more sensitive method in this setting, particularly for inferior wall AMI, because hyperkinetic

myocardium returns toward normal, and myocardium that is hyperkinetic at rest has a reduced capacity to increase its function further during exercise.

Accordingly, the purpose of this study was to evaluate LV function in patients reperfused by intravenous rt-PA or percutaneous transluminal coronary angioplasty, or both. LV function was measured at rest and during maximal exercise using equilibrium-gated radionuclide ventriculography 5 months (range 6 weeks to 9 months) after AMI.

METHODS

Patient enrollment: Patients were enrolled from a clinical trial of rt-PA, the methods of which have been reported in detail.²⁰ All patients presenting to our hospital who fit the criteria were offered rt-PA by protocol, and over 90% accepted. Briefly, enrolled patients were between the ages of 18 and 75 years old, with chest pain typical of angina pectoris that lasted 30 minutes to 8 hours and that was not responsive to nitroglycerin. The pain was accompanied by characteristic electrocardiographic findings of AMI (0.2 mV ST-segment elevation in ≥ 2 leads). Three patients, excluded from the rt-PA trials because of a bleeding disorder or cardiopulmonary resuscitation, were reperfused by angioplasty alone and were included in the present study. Eighty-five patients were eligible for this study because they had received rt-PA or had undergone percutaneous transluminal coronary angioplasty during AMI, and 44 of these participated. Reasons for nonparticipation included 7 deaths, 6 patients with noncardiac disabilities that precluded exercise, 23 who were lost to follow-up and 5 who refused to participate.

Population: Clinical characteristics and exercise test data for the 44 patients in this study are listed in Table I.

Treatment protocols: During AMI, the specific protocols randomized patients in a double-blinded manner to receive intravenous rt-PA (0.75 mg/kg over 60 minutes) or placebo. Coronary angiography was performed at 60, 90 and 120 minutes, and the degree of antero-grade flow in the infarct-related vessel was assessed by the criteria of the Thrombolysis in Myocardial Infarction trial.²¹ Reestablishment of grade 2 or 3 flow on a scale of 0-3 that persisted to the end of the angiographic procedure was the criterion for the infarct-related artery to be considered successfully reperfused. After the first arteriogram (60 minutes), the study was unblinded and percutaneous transluminal coronary angioplasty made available to patients who had received placebo.

A second protocol treated all patients with rt-PA, either 0.75 mg/kg over the first hour followed by 0.5 mg/kg for the next 2 hours or 1.2 mg/kg during the

first hour followed by 0.8 mg/kg during the next 2 hours. Coronary angiography was performed at 45 and 90 minutes. After 90 minutes of therapy, all treatment modalities were made available to the patient. Reperfusion was by rt-PA alone ($n = 10$), percutaneous transluminal coronary angioplasty alone ($n = 3$), or both ($n = 31$).

All patients were treated with 5,000 U of heparin during cardiac catheterization, followed by a maintenance infusion adjusted to keep the partial thromboplastin time at 1.5 to 2 times the control level. Repeat coronary angiography was performed before discharge for clinical indications at the discretion of the patient's primary physician. If, in the opinion of the patient's private physician, there was much myocardium with persistent contraction supplied by critically stenosed coronary arteries, then the patient was referred for percutaneous transluminal coronary angiography (if only 1

such artery was seen) or coronary artery bypass graft surgery (if multiple such arteries were seen).

Exercise radionuclide ventriculography (Figure 1):

This procedure was performed at rest and during maximal supine exercise with a bicycle ergometer²² 5 months (range 6 weeks to 9 months) after AMI.

Both rest and exercise scans were performed with a General Electric STARCAM camera in the modified left anterior oblique view, positioned to provide optimal separation of the right and left ventricles.²³ Exercise was begun at a work load of 25 W and increased by 25-W increments at 4-minute intervals. Imaging was performed during the last 3 minutes of each stage. Symptoms, heart rate and arterial blood pressure were monitored and recorded in each stage.

Rest and exercise LV ejection fraction were determined automatically using the General Electric PAGE cardiac program, developed in collaboration with 1 of

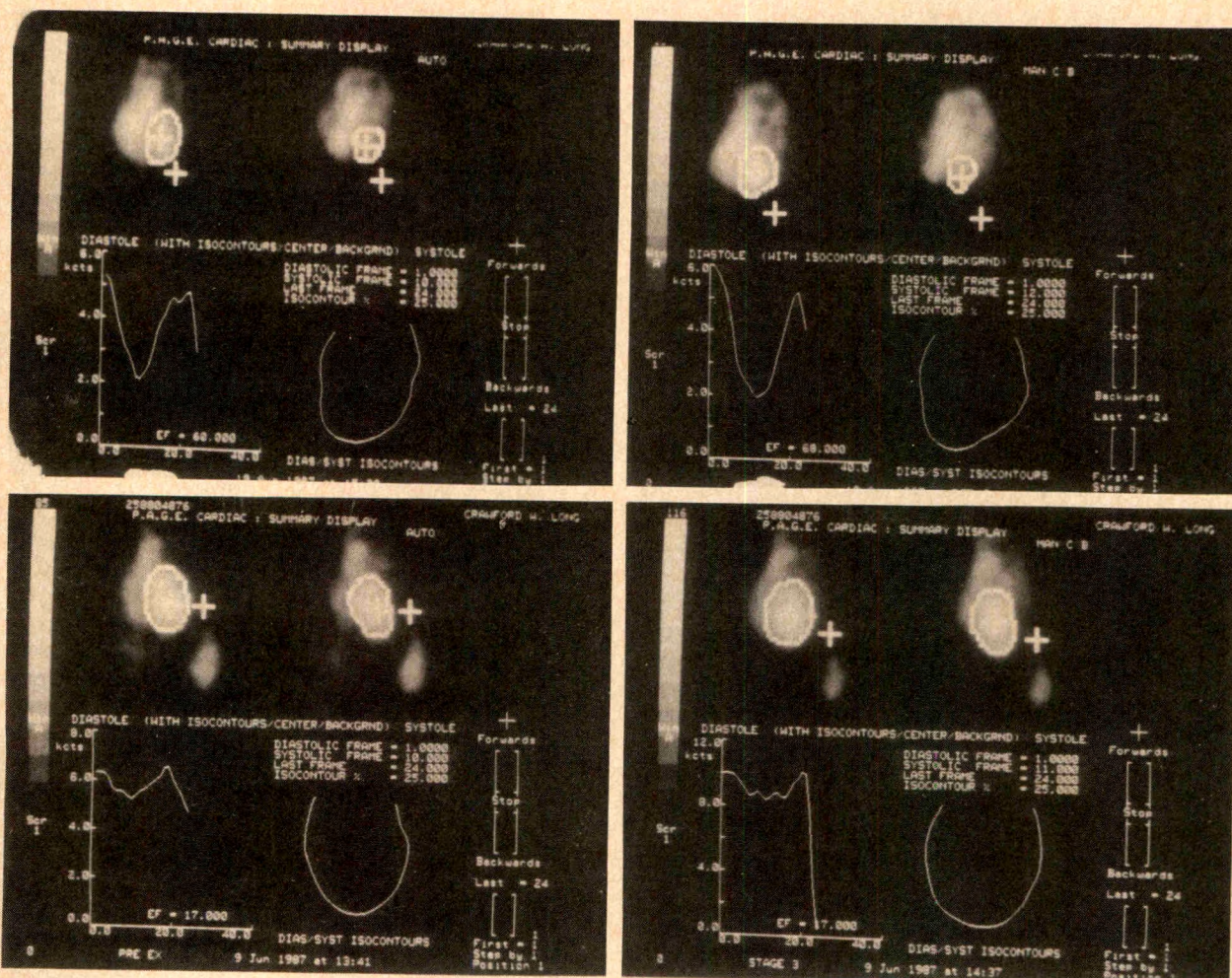


FIGURE 1. Left anterior oblique views of the gated blood pool scans obtained at rest (*left*) and maximal supine bicycle exercise (*right*), with the left ventricular time activity curve and end-diastolic and end-systolic outlines shown below each view, for 1 patient (*above*) with an anterior wall acute myocardial infarction reperfused early and for another (*below*) with an anterior wall acute myocardial infarction reperfused late. Left ventricular ejection fraction (EF) was high at rest or exercise in the patient reperfused early, and increased from rest (*left*) to exercise (*right*) in the patient reperfused early (*above*) but not late (*below*).

our authors (RLE). The end-diastolic (maximal LV counts) and end-systolic (minimal LV counts) frames are determined from the background-subtracted LV images. Ejection fraction is determined as: $100 \cdot (\text{end-diastolic} - \text{end-systolic}) / (\text{end-diastolic})$ counts.

After edge detection, background subtraction and ejection fraction determination, 2 investigators evaluated and confirmed the results of the automatic determinations through (1) an examination of the cine display of the gated cardiac data with edge boundary points superimposed; (2) an evaluation of the background-subtracted left ventricle at diastole and systole to ensure that surrounding chambers or structures were not included in the LV region of interest; (3) an evaluation of the systolic and diastolic images after subtraction of the background-subtracted LV image to ensure that an appropriate level of background counts was subtracted; and (4) evaluation of gating by comparison of the computer-selected heart rate with the simultaneous electrocardiogram and notation of the ratio of computer-rejected to computer-accepted beats. All studies were interpreted by investigators unaware of the clinical status of the patients. LV function was compared on paired cine displays that were not labeled to distinguish rest from exercise studies.

Exercise thallium-201 scintigraphy (Figure 2): After an overnight fast, patients were interviewed by a cardiologist who then supervised a symptom-limited exercise treadmill test according to the Bruce protocol, while a 12-lead electrocardiogram was recorded as described previously.²⁴ The rest electrocardiogram was analyzed for baseline ST-T wave abnormality, evidence

of prior AMI (Q waves >0.03 second that were $\geq 1/4$ the depth of the R wave) and LV hypertrophy.²⁵ The criterion for a positive electrocardiographic response to exercise was 0.1 mV flat or downsloping ST-segment depression 0.08 second after the J point in ≥ 3 consecutive heart beats with a normal baseline ST-T wave segment. If the baseline electrocardiogram was abnormal or if the patient was receiving digitalis, then the test was classified as equivocal if there was ≥ 0.1 mV flat or downsloping ST-segment depression. No patient in this study had normal thallium-201 distribution, was receiving digitalis or had chest pain during the exercise test. In addition, patients were required to reach 85% of age-predicted maximal heart rate to be included in this analysis. The patients were exercised to a symptomatic end point of dyspnea, fatigue or leg discomfort. Patients were not stopped simply because of achieving a target heart rate, but would have been stopped for cardiac arrhythmias or ST-segment depression if it had been >0.25 mV.²⁵ Patients had an intravenous catheter placed before the exercise test and were asked to tell the physician when they felt that they could only exercise for 60 seconds more, at which time 3.5 mCi of thallium-201 was injected.

Tomographic image acquisition and processing:

Immediately after treadmill exercise, patients were seated for a recovery period of 2 to 3 minutes and then walked to a tomographic imaging system (General Electric model 400 AT with Star computer). The gamma camera was positioned to start in approximately the 45° right anterior oblique view and rotated through an anterior 180° arc. Thirty-two planar views were obtained (40 seconds/view). After the initial period of imaging, which required about 22 minutes, the patient was asked to return for delay images 3 hours after the beginning of the first image acquisition.

Before tomographic reconstruction, the images were analyzed for patient motion during acquisition by a program recently developed in this laboratory.²⁶

"Bull's-eye" processing and quantitative analysis (Figure 2): The investigator processing the tomographic thallium-201 data had no knowledge of the patients' clinical status. From the smoothed view data, 1-pixel-thick transaxial slices were reconstructed using a conventional ramp-filtered back-projection algorithm without any attenuation correction (General Electric model 400 AT with Star computer). An oblique-angle slice reconstruction procedure (General Electric model 400 AT with Star computer) and quantitative analysis were performed. Each short-axis slice was subjected to a maximal count circumferential profile analysis.^{24,27} For all slices, except the first 2 apical slices, the maximal count was determined along 40 radial vectors (i.e., 9° angular increments) that emanated from an operator-

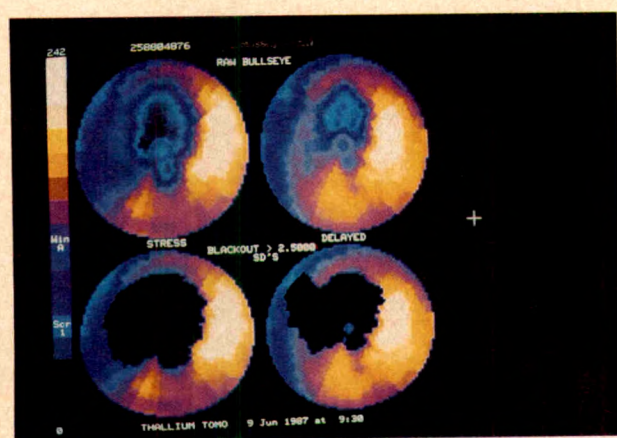


FIGURE 2. Thallium-201 tomography (TOMO) bull's-eye (BULLSEYE) displays at stress (left) and 3-hour delay (right) in 1 patient with an anterior wall defect and no redistribution to indicate anterior wall acute myocardial infarction, with no evidence of ischemia. Bull's-eye displays above show relative counts, whereas displays below show blackened areas over the regions identified as abnormal by comparison with our 50-patient normal file. This patient, like all others in this study, showed no evidence of myocardial ischemia by symptoms or thallium-201 during the exercise test.

defined center of the left ventricle. In contrast to other approaches, no slice-to-slice normalization procedure was forced on the data, so that relative count variations from slice to slice could be appreciated in the quantitative images. This bull's-eye image has the counts corresponding to the apical region in the center, while the counts in the basal region are shown in the outer portions. The bull's-eye image has an inherent fish-eye distortion, so that 1 pixel at the center of the image corresponds to a larger mass (volume) of the myocardium than does a pixel at the periphery of the image.

The normal bull's-eye images reflect the average distribution of thallium-201 from the normal female ($n = 50$) and male ($n = 50$) populations.²⁵

The tomographic thallium-201 studies were interpreted by 2 physicians unaware of the patients' clinical status. Defects were defined as an area over 3% of the total LV area and >3.0 standard deviations below the sex-matched normal file. We defined redistribution as a change of 1.0 standard deviation in severity of the defect between stress and 3-hour delay studies.

Statistical analysis: Ejection fractions were compared between groups of patients using Student's t test for unpaired data, and the change in ejection fraction between rest and exercise was evaluated using Student's t test for paired data.²⁸ The relation between ejection fraction and time of reperfusion was analyzed using linear regression, correlation coefficients and 1-way analysis of variance to determine whether the slope differed from 0.²⁸ A p value <0.05 was required for statistical significance, whereas $0.05 < p < 0.10$ was reported as marginally significant.

RESULTS

Reperfusion was achieved with rt-PA in 31 patients and with percutaneous transluminal coronary angioplasty in 9 patients. Reperfusion was not achieved in 4 patients (9%). Percutaneous transluminal coronary angioplasty was performed after successful reperfusion with rt-PA in 28 patients, and surgical revascularization was achieved in 5 patients.

The relation between the exercise ejection fraction and the time of reperfusion for patients with an anterior wall AMI is shown in Figure 3. Only the exercise ejection fraction for anterior wall AMI demonstrated a significant relation to the time of reperfusion ($r = -0.58$; standard error of the estimate = 11.9%; $p < 0.02$). Ejection fractions both at rest and during exercise were greater for patients with an anterior wall AMI reperfused early (within 4.5 hours) after the onset of chest pain. This time interval was selected by an initial interest in evaluating the effects of rt-PA administered within 4 hours, plus the 0.5 hour required for the opening of the artery, as well as by inspection of the data. The 4.5-

hour time interval was used for subsequent analysis of early and late reperfusion.

Figure 4 demonstrates the change in LV ejection fraction in patients with an anterior wall AMI reperfused early versus late or not at all. The ejection fraction at rest of the patients reperfused early ($44 \pm 8\%$) was significantly greater than that of the patients reperfused late or not at all ($32 \pm 9\%$, $p = 0.004$). In addition, the group reperfused early had an increase in ejection fraction during exercise (to a maximal ejection fraction of $53 \pm 9\%$ with early reperfusion vs $33 \pm 11\%$ with late or no reperfusion; $p = 0.0005$). Of the 8 patients in this early reperfused group, ejection fraction during exercise was increased in 7, and 1 patient developed frequent ventricular premature beats during exercise that prevented accurate gating of the exercise gated blood pool scan.

Among the 12 patients with an anterior AMI who were reperfused after 4.5 hours or not at all, technically satisfactory exercise gated blood pool scans were obtained in 11. Only 3 of these had an increase in ejection fraction with exercise. Overall, the mean ejection fraction at rest in this group ($32 \pm 9\%$) was unchanged by exercise ($32 \pm 11\%$).

There was no difference in congestive heart failure, previous AMI, hypertension or valvular heart disease

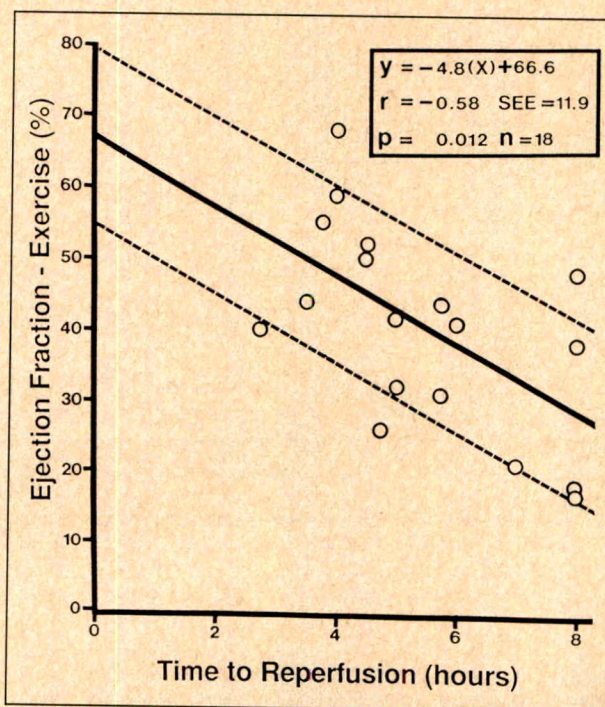


FIGURE 3. Relation between exercise ejection fraction and time to reperfusion (time from onset of chest pain to documented reperfusion). Patients were studied about 5 months after anterior wall acute myocardial infarction. Reperfusion was not successful in 3 patients, whose data are plotted at 8 hours. Technical problems precluded exercise data in 2 patients. Each circle represents 1 patient. NS = difference not significant; SEE = standard error of the estimate.

between the patients reperfused early and late (Table I).

Among the patients with an inferior wall AMI, no subset showed a correlation between time to reperfusion and exercise ejection fraction (Figure 5) or ejection fraction that was improved by early reperfusion at rest or during exercise (Figure 6). The ejection fraction at rest ($43 \pm 9\%$) increased with exercise in 18 patients and was significantly higher during exercise for the group as a whole ($49 \pm 13\%$, $p < 0.004$).

DISCUSSION

The results of the present study of 44 patients demonstrate improved LV function at rest and exercise 5 months (range 6 weeks to 9 months) after administration of rt-PA to interrupt AMI. Improvement was limited to patients who had an anterior AMI and to those whose infarct-related artery was revealed by angiography to be patent within 4.5 hours of the onset of chest pain. In contrast, all patients with an inferior wall AMI and those with an anterior wall AMI in whom patency

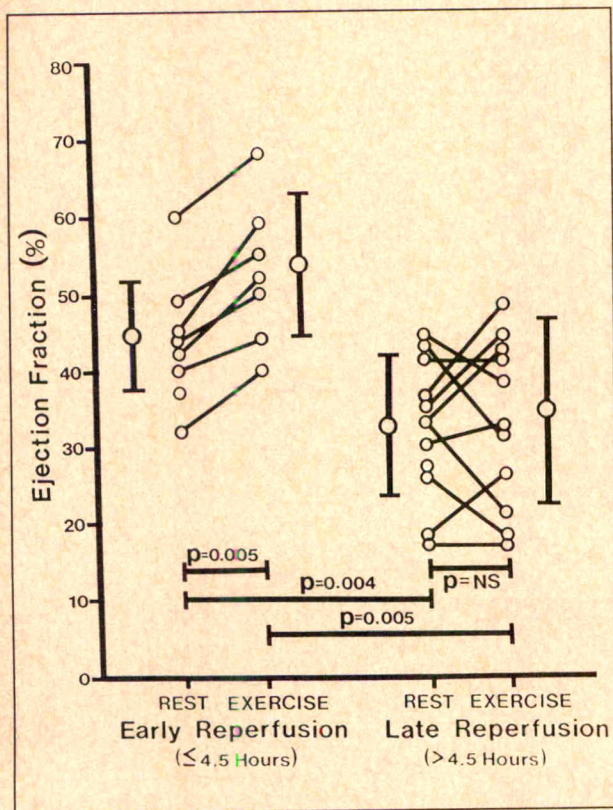


FIGURE 4. Left ventricular ejection fraction at rest and exercise in 2 groups of patients studied several months after an anterior wall acute myocardial infarction. The group on the left had documented reperfusion early (≤ 4.5 hours after onset of chest pain), and the group on the right had reperfusion either late or not at all. Note higher ejection fractions at rest and exercise after early reperfusion by recombinant tissue-type plasminogen activator or angioplasty. NS = difference not significant.

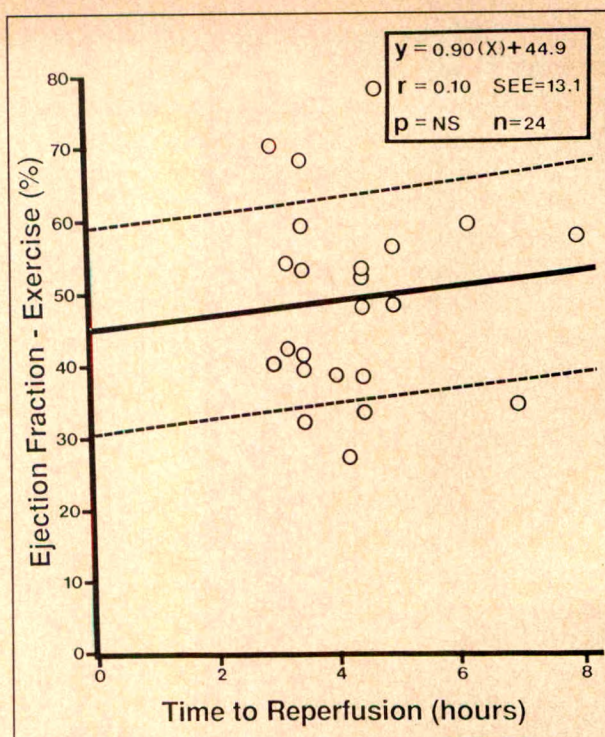


FIGURE 5. Lack of relation between exercise ejection fraction and time to reperfusion in patients studied about 5 months after an inferior wall acute myocardial infarction. Reperfusion was unsuccessful in 1 patient whose data are plotted at 8 hours. Abbreviations as in Figure 3.

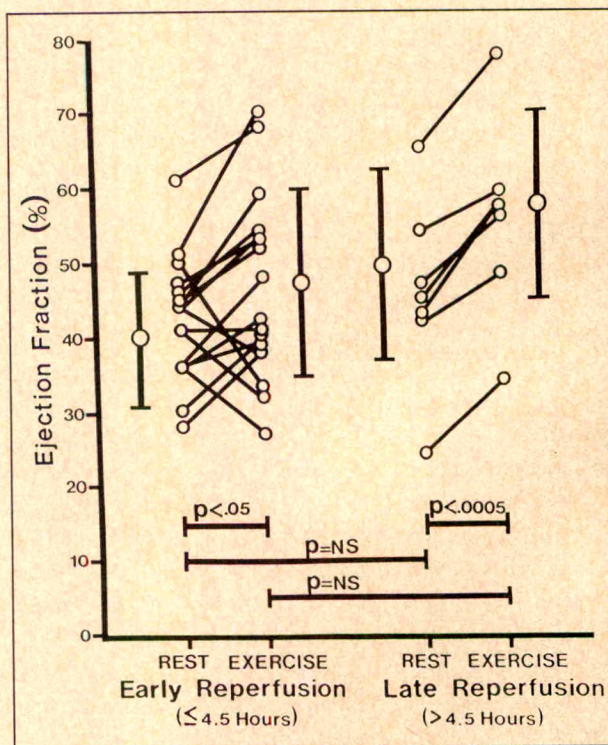


FIGURE 6. Left ventricular ejection fraction at rest and exercise in 2 groups of patients studied several months after an inferior wall acute myocardial infarction. There was no significant difference (NS) in ejection fractions between patients with early (left) versus late (right) reperfusion.

was proved only after 4.5 hours or not at all had no improvement in LV function at either rest or exercise. These results seem particularly significant because the time requirement for early reperfusion was expressed here as the time from onset of chest pain to angiographically documented restoration of flow.

The evaluation of LV function in this study was performed not only at rest but also during maximal, symptom-limited exercise. Global LV function at rest may be compensated for in the early weeks after AMI by hypercontractility of the noninfarcted segments.^{18,19} LV function during exercise would be expected to be a marker of greater sensitivity in the detection of abnormalities than would function at rest, because hypercontractile myocardium at rest could not improve much with exercise.²² Also, hypercontractility should not have been present at the time of our studies (6 weeks to 9 months after AMI). Although accurate analysis of regional LV function could help detect this differential function of noninfarcted versus infarcted regions,¹⁷⁻¹⁹ the response of global function to exercise is probably more important to long-term prognosis.²⁹ Moreover, analysis of regional LV function by a single planar gated blood pool scan has several difficulties. First, acquisition of the gated blood pool scan during exercise is essentially limited to the left anterior oblique projection in order to ensure accurate measurement of LV ejection fraction,²² and this projection offers limited assessment of regional LV function (Figure 1). Second, the number of counts that can be acquired during exercise is limited, and this limits analysis of regional LV function.

Use of exercise LV ejection fraction to assess the late effects of myocardial reperfusion on cardiac function could be confounded if the patient developed myocardial ischemia during the exercise test.²² Exercise-induced ischemia has been shown to produce a decrease in ejection fraction between rest and exercise.²² Thus, to ensure that we could interpret differences in LV function during exercise as indicators of differences in the extent of permanent myocardial damage, we tried to exclude the possibility of myocardial ischemia. First, all patients underwent revascularization where clinically indicated by percutaneous transluminal coronary angioplasty (37 of 44) or coronary bypass surgery (5 of 44), or both. Second, no patient had evidence of ischemia by chest pain or redistribution of a tomographic thallium-201 defect on symptom-limited exercise to $\geq 85\%$ of age-predicted maximal heart rate (Figure 2). Also, many patients were receiving cardiac medications to prevent ischemia at the time of the study. Thus, these factors should minimize the possibility that exercise-induced myocardial ischemia influenced LV functional reserve. Finally, to avoid the influence of myocardial

"stunning" on function,³⁰ all studies were performed 6 weeks to 9 months after AMI. Thus, the differences in exercise ejection fraction should primarily reflect the extent of infarction.

Measurements of LV function at rest and during maximal exercise demonstrated different responses in patients who had an anterior versus an inferior wall AMI. Reperfusion of anterior but not inferior wall AMI within 4.5 hours resulted in improved LV function at rest and during exercise, compared with anterior AMI reperfused later (Figures 3 and 4). This finding is consistent with that of a recent study by Guerci et al,¹⁵ which reported improved regional LV function among anterior wall AMI patients in whom rt-PA treatment was initiated during the first 4 hours of chest pain. Exercise ejection fraction was also improved in that study when all patient data were combined, but results were not reported for subsets with anterior versus inferior wall AMI. The largest study of thrombolytic therapy, however, reported improved survival only in patients with an anterior wall AMI.²

Among patients with an inferior wall AMI, rest and exercise LV function was similar, regardless of the time of reperfusion (Figures 5 and 6). Previous studies of LV function after reperfusion have produced conflicting results. White et al's¹⁴ randomized trial of streptokinase and placebo demonstrated an improved ejection fraction at rest among patients with an inferior AMI. Alternatively, neither the Thrombolysis in Myocardial Infarction trial²¹ nor the Western Washington (streptokinase in acute infarction) randomized trial⁴ reported improved global LV ejection fraction at rest among patients with a reperfused inferior wall AMI. The Thrombolysis in Myocardial Infarction trial did report improved regional LV function.²¹ Bates et al³¹ reported serial improvement in LV function at rest after inferior wall AMI only when treatment was initiated in the first 2 hours. The authors of the Second International Study of Infarct Survival recently reported improved LV function during exercise after early reperfusion.¹⁶ None of our patients with an inferior wall AMI achieved reperfusion before 3 hours of symptom-onset, and they had no benefit in LV function.³¹ Perhaps our patients with proven reperfusion in <4.5 hours were not improved, compared with patients with late or no reperfusion, in part because all patients underwent revascularization if indicated by clinical and angiographic data. Thus, our "control group" with late or unsuccessful reperfusion may have been improved compared with the control group in the Second International Study of Infarct Survival.¹⁶ This suggestion is supported by the increase in LV ejection fraction during exercise in our control group with inferior wall AMI.

The present study did show a significant linear correlation ($r = -0.58$; standard error of the estimate = 11.9%; $p < 0.02$) between exercise ejection fraction and time from onset to reperfusion of anterior wall AMI. Thus, the present study reveals that the improvement in LV functional reserve is closely related to the rapidity with which coronary blood flow is restored in patients with an anterior wall AMI. The same analysis revealed no significant correlation between exercise ejection fraction and time to reperfusion of inferior wall AMI ($r = 0.10$; difference not significant).

The reasons for the different functional responses to early reperfusion between anterior versus inferior wall AMI cannot be fully explained by the present study. The most likely reason suggested by the present data, however, is that inferior wall AMI causes less extensive LV damage and functional impairment than does anterior wall AMI. Also, our control group had revascularization when indicated after late rt-PA. In the group of patients reperfused after 4.5 hours, or not at all, ejection fractions were higher in patients with an inferior wall (Figures 5 and 6) versus an anterior wall (Figures 3 and 4) AMI at rest (46 ± 12 vs $32 \pm 9\%$, $p < 0.05$) and exercise ($55 \pm 12\%$ vs $33 \pm 11\%$, $p < 0.01$). Early reperfusion of anterior AMI resulted in values of ejection fraction at rest ($44 \pm 8\%$) and exercise ($53 \pm 9\%$) that were not different from values for inferior AMI reperfused late or not at all, at rest ($46 \pm 12\%$) or exercise ($55 \pm 12\%$). Thus, early reperfusion of anterior wall AMI resulted in LV function and reserve capacity comparable to those of inferior wall AMI reperfused late or not at all. That even exercise ejection fraction showed no difference in inferior wall AMI reperfused early versus late may be because the extent of the inferior wall AMI was too small to be limited further by early reperfusion or because even exercise ejection fraction was not sufficiently sensitive to detect a small reduction in the extent of AMI. It should also be noted that the group of patients with an inferior wall AMI who had reperfusion early are being compared in this study primarily with patients reperfused successfully only 2 hours later. Thus, the present comparison might underestimate the ability of reperfusion to salvage myocardium and preserve LV function. Conversely, the same considerations indicate the significance of finding improved LV function after early reperfusion of anterior wall AMI. The different responses to early reperfusion could not be explained by differences in clinical characteristics or exercise data (Table I).

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Frequency and Significance of Occult Late Potentials on the Signal-Averaged Electrocardiogram in Sustained Ventricular Tachycardia After Healing of Acute Myocardial Infarction

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The quantitative and morphologic characteristics and significance of late potentials on the signal-averaged electrocardiographic QRS complex remain unknown. To assess this, the signal-averaged electrocardiogram of 48 patients (mean age \pm standard deviation 62 ± 9 years) with sustained ventricular tachycardia (VT) after healing of acute myocardial infarction and late potentials were analyzed. Late potentials could be classified into 3 morphologic subtypes: type I late potentials (19 patients, 40%) occurred in the terminal 40 ms of the QRS complex; type II late potentials (16 patients, 33%) started before the end of the QRS complex and extended 30 ± 17 ms into the ST segment; type III late potentials (13 patients, 27%) started after the end of the QRS complex in the ST segment and ended 67 ± 27 ms after the end of the QRS complex. The amplitude of the late potentials in type III, when compared with types I and II, was significantly lower, whereas the QRS duration on the electrocardiogram in type I, when compared with types II and III, was significantly longer. Computer algorithm based on noise failed to identify most type III late potentials. No difference was noted in age, sex, site of the myocardial infarction, and rate of induced VT among the 3 types. It is concluded that (1) morphologic types of late potentials are likely a function of anatomic and geometric differences with resultant differences in

conduction; (2) occult late potentials (type III) are seen in 27% of patients with sustained VT after healing of acute myocardial infarction and likely reflect activation of a smaller mass of muscle bundles with a smaller extracellular field, as compared with type I and II late potentials; and (3) because type III late potentials are often missed by computer algorithms based on noise, they are better suited for qualitative analysis.

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In recent years, the signal-averaged electrocardiogram has emerged as a useful noninvasive tool for detecting the substrate in patients who are suspected of having reentrant ventricular tachyarrhythmias.¹ Abnormalities in the signal-averaged electrocardiogram have been described in patients with sustained monomorphic ventricular tachycardia (VT) associated with coronary artery disease,² cardiomyopathy, and even in some patients without evident organic heart disease.³⁻⁵ Furthermore, the presence of an abnormal signal-averaged electrocardiogram has been correlated with inducibility of sustained VT in the laboratory.⁵⁻⁸ Abnormalities in the signal-averaged electrocardiogram have been expressed qualitatively as well as quantitatively. Generally, abnormalities occur in the terminal portion of the QRS complex,² referred to as "late potentials"; however, not unusually, abnormal potentials may occur later in the ST segment.⁹ Little is known about the incidence, morphologic characteristics and significance of such "late" late potentials. This study defines these late late potentials and assesses their clinical significance.

METHODS

Patients: The study group consisted of 48 patients (mean age \pm standard deviation 62 ± 9 years) who had spontaneous and inducible, sustained VT in the setting of an old myocardial infarction. No patient had

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bundle branch block. All had an abnormal signal-averaged electrocardiogram (qualitative or quantitative parameters).

Signal-averaging technique: Signal averaging on the surface electrocardiogram was performed before electrophysiologic testing. All antiarrhythmic agents were withheld for ≥ 6 half-lives before the study. Seven silver/silver chloride electrodes were attached after the skin was cleaned with alcohol, to constitute 3 orthogonal bipolar electrodes as follows: the horizontal X electrodes in the right and left midaxillary lines at the fourth intercostal space, the vertical Y electrode in the suprasternal notch and V_3 position, and sagittal Z electrodes in the V_2 position anteriorly and corresponding position posteriorly.

The instrument used records X, Y and Z signal components that are amplified, digitized and recorded. In all patients, ≥ 199 beats were averaged and data processed with a bidirectional 4-pole, high-pass Butterworth filter, with a high-frequency cutoff of 250 Hz and low-frequency cutoff at 40 Hz. A vector magnitude (V) was calculated for each point of the averaged X, Y, Z signal as $V = \sqrt{X^2 + Y^2 + Z^2}$. The beginning of the QRS was identified by a standard commercial algorithm at the beginning of acquisition on the basis of 8 consecutive averaged beats designed to mimic visual determination of the onset of the QRS complex.

The end of the QRS complex was identified in a manner similar to that described by Simson.² The root-mean-square voltage was calculated for the terminal 40 ms of the QRS. In addition, the duration of low-amplitude signals of $<40 \mu V$ and the duration of the entire signal-averaged QRS complex was calculated by the computer algorithm.

The signal-averaged electrocardiograms were further analyzed qualitatively, individually and independently by 2 of the investigators so as to define (1) the end of high-frequency signals: the end of high-frequency signals was determined visually and subjectively at a point where a distinct pattern of signals was recorded at twice the visually determined baseline level; and (2) location of "late potentials" as to its spatial relation with the vector magnitude. A consensus was reached on these definitions before further analysis. The following parameters were then computed:

Magnified vector magnitude of high-frequency signals with a band width of 40 to 250 Hz was plotted so as to give 1-mm deflection for each microvolt signal at a paper speed of 400 mm/s.

Definition of terms: DURATION OF HIGH-FREQUENCY SIGNALS: The duration of high-frequency signals as seen on vector magnitude plots was measured in milliseconds between onset and offset points, as described earlier.

QRS DURATION: This duration was measured in milliseconds of magnified unfiltered analog signals of the surface electrocardiogram.

DURATION OF LOW-AMPLITUDE SIGNALS: Duration of low-amplitude signals was measured in milliseconds from the offset of the vector magnitude plot to a point where signals exceeded $40 \mu V$. By subtracting the corresponding QRS duration from the duration of low-amplitude signals, the duration of late potentials beyond QRS was derived.

VOLTAGE IN THE TERMINAL 40 MS: Amplitude of the terminal 40-ms portion of the vector magnitude plot expressed in microvolts was either measured as root-mean-square voltage or peak voltage. Signal-averaged complexes were also analyzed morphologically to define the location of late potentials in relation to analog recordings of the QRS complex.

Statistical analysis: This was performed by 1-way analysis of variance and chi-square analysis when appropriate.

RESULTS

Morphologic characteristics of late potentials: On morphologic analysis of the signal-averaged electrocardiograms and by redefining the end of high-frequency QRS, 3 distinct patterns of late potentials emerged:

TYPE I: The type I pattern was where almost all of the high-frequency signals were located inside the surface electrocardiogram and late potentials were seen in the terminal portion of the QRS complex. In all patients late potentials ended <10 ms beyond the end of the surface QRS complex (Figure 1A). Type I late potentials occurred in 19 of 48 patients (40%). Typically, duration of the QRS complex was prolonged and encompassed the entire duration of the vector complex (Figure 1A). The root-mean-square voltage of the terminal 40 ms of type I late potentials was typically higher with an average value of $13 \pm 7 \mu V$.

TYPE II: Late potentials occurred in the terminal QRS complex but extended beyond the QRS complex within the ST segment. Obviously, high-frequency signals were noted beyond the analog electrocardiographic complex. A typical example of type II late potentials is shown in Figure 1B. Here, the late potentials can be clearly seen to begin in the terminal portion of the QRS and extend far beyond the end of the QRS. Type II late potentials occurred in 16 of 48 patients (33%).

TYPE III: The type III pattern was where abnormal high-frequency, low-amplitude signals were seen to begin after the surface electrocardiogram appeared to be completed (Figure 1C). When compared with types I and II, the principal vector magnitude of high-frequency signals in type III has a sharp cutoff, coinciding with

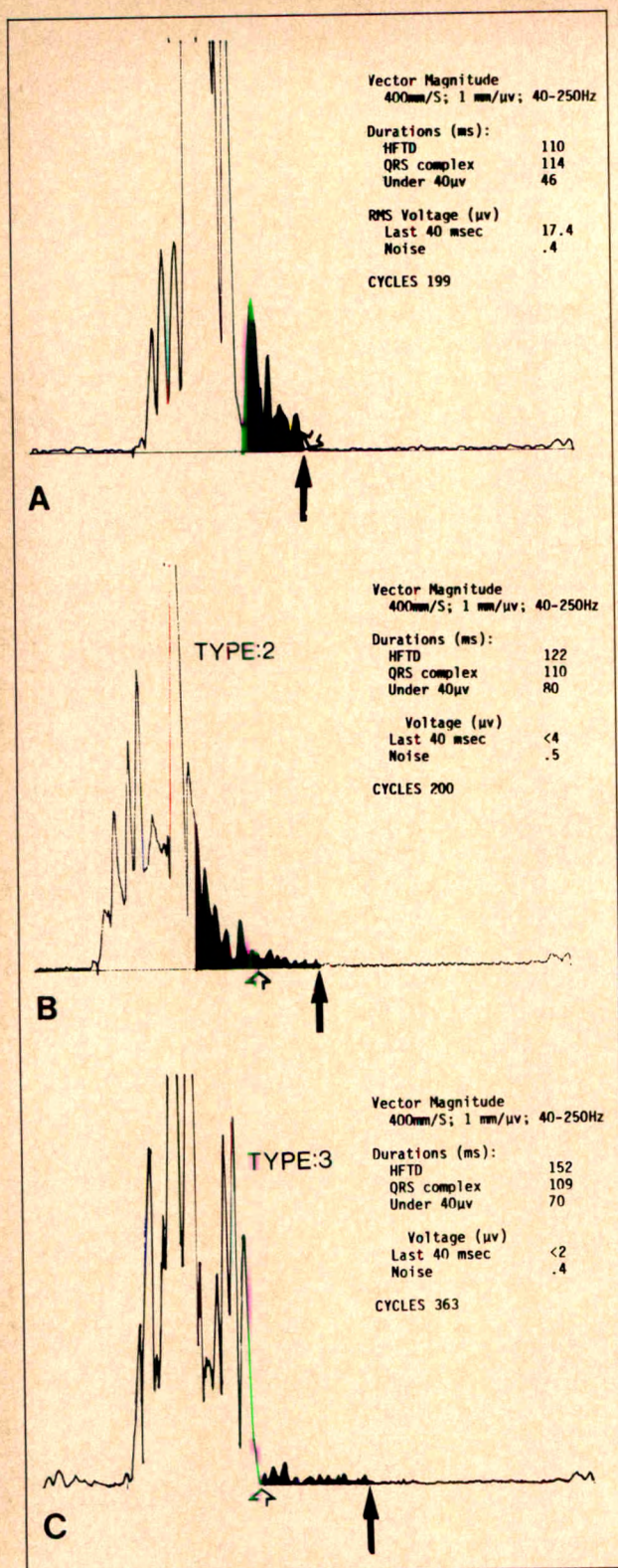


FIGURE 1. Vector magnitude plot of high-frequency signals showing the 3 types of late potentials. **A**, example of type I late potential. Note that the QRS duration is prolonged (offset marked by an open arrow) and encompasses the entire late potentials (shaded area); **B**, type II late potentials (shaded area) is seen to begin before the offset of the QRS (open arrow) and extends into the ST segment; **C**, type III late potential (shaded area) is seen to begin after the end of QRS (open arrow) and continues into the ST segment. Note low-amplitude of type II and particularly of type III late potentials.

TABLE I Signal-Averaged Parameters in the Three Types of Late Potentials

Signal-Averaged Parameters (40 Hz)	Late Potential Type			p Value
	I	II	III	
QRS duration (ms)	132 ± 25	106 ± 12	99 ± 12	<0.0001
High-frequency total duration (ms)	141 ± 2	136 ± 24	161 ± 27	<0.25
Duration of LAS beyond QRS (ms)	8 ± 8	30 ± 17	61 ± 27	<0.0001
Duration of LAS (ms)	53 ± 23	60 ± 27	84 ± 39	<0.002
Voltage in the terminal 40 ms (V40) (μV)	13 ± 7*	<10 ± 7†	<4 ± 2†	<0.0006

* Root-mean-square voltage.

† Peak voltage.

LAS = low-amplitude signals.

the end of the QRS, as seen on the surface electrocardiogram. This was followed by relatively very low-amplitude signals, but distinct from baseline noise, and extending for a variable period. Type III late potentials were seen in 13 of 48 patients (27%).

Quantitative parameters of late potential subtypes:

When signal-averaged electrocardiographic parameters were compared, the subtypes appeared to be significantly different from each other (Table I). In type I late potentials, the electrocardiogram QRS complex was significantly prolonged, as compared with types II and III. On the other hand, although the duration of high-frequency signals was longer in type III than in types I and II, these differences were not statistically significant. The duration of low-amplitude signals <40 μV was also significantly different in these subtypes. In type I late potentials, the low-amplitude signals did not extend substantially beyond the QRS complex. In contrast, in types II and III late potentials, low-amplitude signals extended far beyond the QRS complex. However, in type II, late potentials began in the terminal QRS, whereas in type III, they began after the end of QRS. The late potentials in types II and III were of significantly smaller amplitude than those in type I.

Clinical features: Twenty of 48 patients (42%) had an anterior wall myocardial infarction, 21 of 48 (44%) had an inferior wall myocardial infarction and 7 of 48 (14.5%) had mixed sites of prior myocardial infarctions. When various parameters like site of infarction, induced rate of VT and mode of VT induction were analyzed, there were no statistically significant differences between the 3 types (Table II).

Identification of type III late potentials by computer

algorithm: Type III late potentials appeared as a distinct subtype, not only from a morphologic point of view, but also because 62 to 70% of these type III late potentials were not identified by computer-based algorithms (Figure 2, A and B). Computer algorithms underestimated the duration of low-amplitude signals by 20 to 72.5 ms (Figure 2, A and B).

DISCUSSION

Asynchronous ventricular activation due to inhomogeneous, delayed conduction of an impulse through scarred myocardium¹⁰⁻¹² has been shown to generate high-frequency, low-amplitude signals measuring only a few microvolts.¹³ These have been shown to be due to depolarization of surviving myocardial cells that have been uncoupled and electrically isolated by intervening fibrous tissue.¹⁴ Detection of late potentials on the signal-averaged electrocardiogram requires that activation of ventricular myocardium in the region of the substrate must outlast normal ventricular activation to be apparent at the end of QRS. Alterations in the initial portion of the signal-averaged electrocardiogram in patients with VT have also been described.¹⁵

Current observations and mechanisms of late potentials: The present study was initiated based on our observations of distinct morphologic differences in late potentials and failure to detect abnormalities by computer algorithm. Three distinct types of late potentials could be identified. Type I late potentials were usually seen in the setting of a broad QRS, >110 ms (132 ± 25 ms). Abnormalities were confined to the QRS complex and the amplitudes of late potentials were relatively higher than in types II and III. Superimposition of intraventricular delay on substrate activation may be responsible for late potentials of higher amplitude which were confined to the QRS complex.

Because type III late potentials are of very low amplitude, they most likely reflect activation of a smaller mass of muscle bundles with a smaller extracellular field than types I and II, and thus may be missed com-

TABLE II Clinical Features of Patients with Different Types of Late Potentials

	Late Potential Type		
	I	II	III
Age (yr)	61 \pm 11	62 \pm 8	62 \pm 10
Site of MI			
Anterior wall	8/19 (42%)	7/16 (43%)	5/13 (38%)
Inferior wall	8/19 (42%)	6/16 (37%)	7/13 (54%)
Mixed MI	3/19 (16%)	3/16 (19%)	1/13 (8%)
Induced VT rate (beats/min)	206 \pm 34	198 \pm 50	221 \pm 45
Mode of VT induction			
S ₁ S ₂	2 (11%)	—	1 (8%)
S ₂ S ₃	9 (30%)	12 (80%)	9 (69%)
S ₃ S ₄	7 (39%)	3 (20%)	3 (23%)

MI = myocardial infarction; VT = ventricular tachycardia.

pletely, unless the noise level is quite low. An average noise level of $0.4 \mu\text{V}$ in the present study might have helped to identify type III late potentials. In a recent study,¹⁶ reduction of noise level to $0.3 \mu\text{V}$ was shown to improve sensitivity in detecting late potentials without sacrificing specificity. Because a basic abnormality is increased duration of low-amplitude high-frequency signals, some have suggested the use of low-amplitude signals beyond QRS, i.e., high-frequency total QRS duration minus QRS duration as a useful parameter.¹⁷ This parameter was most abnormal in type III late potentials, where the signals extended 61 ± 27 ms beyond QRS. This duration was underestimated by 20 to 72.5 ms when computer algorithms alone were used to analyze late potentials. Thus, although these subtypes appear very distinct in their quantitative parameters as well as morphologic appearances, when clinical features

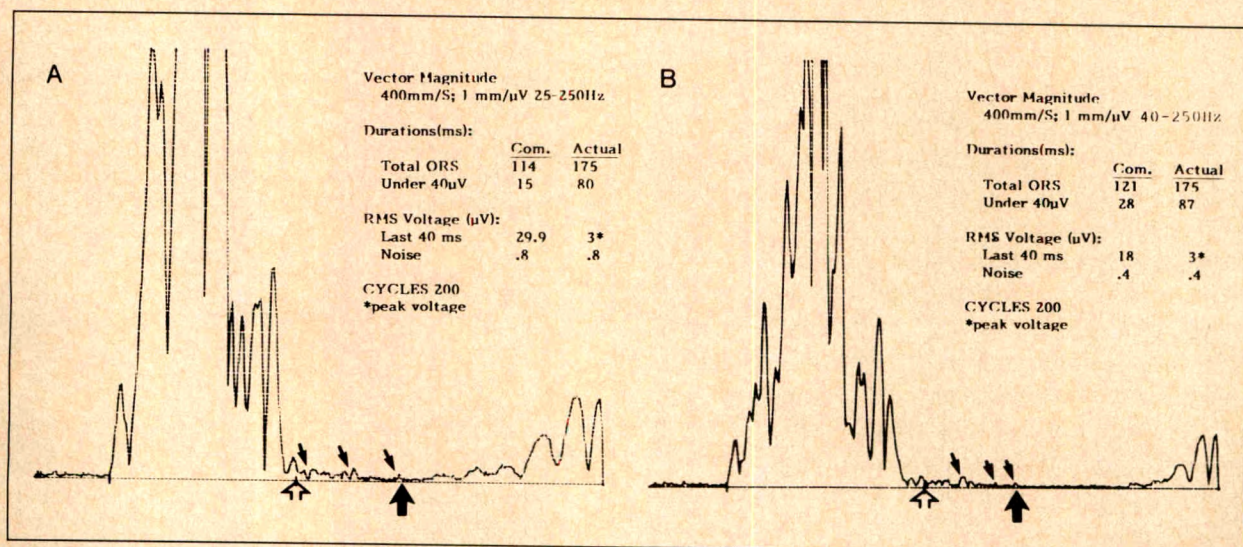


FIGURE 2. Effect of visual determination of offset of high-frequency signals. Type III late potentials are shown here by narrow dark arrows. Although late potentials are more evident at 25 Hz (A), they can clearly be identified even at 40 Hz after significant noise reduction to $0.4 \mu\text{V}$, beyond the offset (open arrow) which is determined by noise-based computer algorithm (B). True offset of late potentials is marked by broad dark arrow. Note the underestimation of the duration of late potentials by computer algorithm (Com.) both at 25 Hz (A) and 40 Hz (B). HFTD = total duration of high-frequency signals; RMS voltage = root-mean-square voltage.

were compared, no difference was found between these subtypes. This suggests that the type of late potential is a function of anatomic and geometric differences (surviving Purkinje muscle mass/fibrotic Purkinje muscle mass/extracellular field) between the types, with resultant differences in conduction.

Previous studies: Because degree of delay of ventricular myocardium activation in areas of the substrate have been correlated with the ability to detect late potentials on the signal-averaged electrocardiogram,¹⁸ one would expect their presence, at least in a few patients, to be found late in the ST segment. In fact, initial work by Berbari et al¹³ in the animal model showed the presence of such late potentials in the ST segment of beats preceding ventricular arrhythmias. Subsequent work in humans by Simson² revealed late potentials only in the terminal portion of the QRS. However, Rozanski et al⁹ did find high-frequency signals early in the ST segment that disappeared after aneurysmectomy for control of VT. These differences may have been due to different filter designs or electrode configurations, as suggested by Simson,² but may also have been due to failure of the computer algorithm, based on noise detection, to properly identify the end of the high-frequency signals as demonstrated in this study. This suspicion is further strengthened by identification of late potentials in the ST segment by other investigators who relied on visual inspection of signal-averaged electrocardiographic records. Breithardt et al,¹⁹ when quantifying LP activity, determined the onset of late potentials in 2 ways: (1) either finding an isolation point that clearly separated the end of the QRS from the onset of late potential activity; or (2) by defining a point at which the QRS amplitude markedly exceeded the amplitude of mid- and terminal portions of late potentials to the point where low-amplitude signals exceed by 2 to 3 times the baseline noise contained late in the ST segment. However, use of the former definition would result in lower sensitivity in detecting type I and II late potentials in the vector magnitude.

Clinical implications: Multiple quantitative parameters have been suggested to identify abnormal late potentials with variable sensitivity and specificity. Although such parameters based on computer algorithms have been used extensively with remarkable success, reliance solely on computer analysis may result in missing significant abnormalities in the signal-averaged electrocardiogram. As noted before, the offset of high-frequency signals needs to be visually confirmed, or the computer algorithm to identify the end of the filtered QRS complex needs to be improved so as not to miss type III late potentials. Once the end of the filtered

QRS is visually identified, then quantitative parameters can be recalculated.

Limitations of study: (1) Because the amplitude in type II and III late potentials was very low, we expressed it as peak voltages. Although not comparable with root-mean-square voltage of type I late potentials, the difference is striking and should not affect the findings. (2) Regional determinant of offset of high-frequency signals is subjective and may not be reproducible. In the present study, 2 of the investigators independently assessed the offset and a consensus was reached before reaching conclusions. (3) Because morphologic subtyping of late potentials was made by visual comparison of magnified unfiltered surface electrocardiogram with high-frequency signals on the vector magnitude plot, the QRS durations may generally be slightly higher than the nonmagnified surface electrocardiogram recorded at usual paper speed. However, this should not affect the results, because the effect of magnification should be uniform.

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Usefulness of the Automatic Implantable Cardioverter Defibrillator in Improving Survival of Patients with Severely Depressed Left Ventricular Function Associated with Coronary Artery Disease

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Clinical outcome was analyzed among a group of 39 consecutive patients with coronary artery disease, left ventricular (LV) ejection fractions <30% and arrhythmias that required an automatic implantable cardioverter defibrillator (AICD) in an attempt to better define the role of the device in patients with severely depressed LV function. Twenty-nine (74%) were survivors of out-of-hospital cardiac arrest and 10 (26%) had ventricular tachycardia that was refractory to electrophysiologically guided antiarrhythmic therapy. The study group had the following demographic characteristics: 90% were men, mean age was 64 years (range 41 to 79) and mean LV ejection fraction was $21 \pm 4\%$. Concomitant pharmacotherapy included antiarrhythmic drugs in 31 (79%), vasodilators in 22 (56%) and digoxin in 20 (51%). There was no statistical difference in baseline characteristics between survivors and nonsurvivors. Patients were followed for a mean of 24 months (range 2 to 72) from implantation. The difference between actuarial survival—77% at 1 year and 72% at 2 years—and projected survival without the AICD (patients who survive without appropriate device discharge)—30% at 1 year and 21% at 2 years—was significant ($p < 0.01$ and < 0.05 at 1 and 2 years, respectively). This study suggests

that the AICD improves survival in patients with coronary artery disease despite severely depressed LV function.

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The automatic implantable cardioverter defibrillator (AICD) was introduced in 1980 for the treatment of patients with recurrent, potentially fatal arrhythmias who had failed to be adequately protected by pharmacologic or surgical interventions.¹ Subsequent clinical trials have shown the device to be highly effective for terminating lethal arrhythmias and for offering significant long-term survival to cardiac arrest survivors and patients with drug-refractory ventricular tachycardia.^{2–7} In this study, we report use of the AICD in patients with severely depressed left ventricular (LV) function who are survivors of out-of-hospital cardiac arrest or drug-refractory ventricular tachycardia, or both.

METHODS

Patients: The study group comprised 39 patients with coronary artery disease and LV ejection fraction <30% who had an AICD implanted at the University of Miami/Jackson Memorial Medical Center or the Miami Veterans Affairs Medical Center between January 1984 and November 1989. Twenty-nine patients (74%) were survivors of out-of-hospital cardiac arrest. The remaining 10 patients (26%) had recurrent sustained ventricular tachycardia refractory to electrophysiologically guided antiarrhythmic therapy. Criteria for AICD implantation were: (1) recurrent cardiac arrest or recurrent symptomatic sustained ventricular tachycardia with a drug regimen predicted to be successful by prior program electrical stimulation studies;

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(2) failure of 2 drugs or drug combinations or of LV aneurysm resection with subendocardial resection to prevent inducible arrhythmias after documented clinical ventricular tachycardia associated with cardiovascular collapse, or after ventricular fibrillation; or (3) out-of-hospital cardiac arrest with clinical markers of high risk of recurrence even if not inducible by program stimulation studies. Patients in whom ventricular tachycardia or ventricular fibrillation occurred only in an acute phase of myocardial infarction were not AICD candidates. AICD implantation and replacement procedures were accomplished by standard surgical techniques.⁸ One patient whose demographic data were similar to those of our study group died the day after coronary bypass surgery and AICD implantation, and was not included in this analysis.

Patient evaluation: To define the anatomic and electrophysiologic status of each patient, thorough diagnostic evaluation, including cardiac catheterization with coronary arteriography and electrophysiologic studies, and echocardiography or nuclear ventriculography, or both, were performed at our institution or at the referring institution.

Follow-up: From January 1984 to January 1990, all patients were followed in the AICD clinics at the University of Miami/Jackson Memorial Medical Center and the Miami Veterans Affairs Medical Center. The few patients who moved out of the vicinity of our Medical Center have been followed by their local cardiologists.

Follow-up information: Follow-up information is continuously updated by cardiologists in our AICD clinic or cardiologists to whom patients were referred in the community, or both. Follow-up procedures included bimonthly visits up to 1 year, with monthly visits thereafter. We maintained a record of all clinical symptoms attributable to arrhythmias, the cumulative number of AICD discharges, and the patients' clinical status.

Definitions: Appropriate shocks, defined as those preceded by symptoms of ventricular arrhythmia or documentation by concurrent monitoring, or both, were tabulated. In patients who had no symptoms preceding shocks, subsequent ambulatory monitoring was performed to determine whether shocks were appropriate. Inappropriate shocks, those occurring in the absence of symptoms or exercise, or those triggered by supraventricular tachycardia on monitoring, were excluded from analysis. The end points of the study were appropriate shock, sudden death and total mortality. Sudden death was defined conventionally as death within 1 hour of onset of an abrupt change in symptoms. When patients died suddenly, attempts were made to obtain further

data, to distinguish between tachyarrhythmic death and other mechanisms.

Data collection and statistical analyses: All records on the clinical status of patients at the time of implantation, the time of first shock and the long-term outcome of sudden or total death were maintained by investigators. The mechanisms of death (sudden: arrhythmic, nonarrhythmic; nonsudden: cardiac, noncardiac) were evaluated.⁹ True survival, as well as projected survival without the AICD (patients who survived without an appropriate AICD discharge), was calculated by Kaplan-Meier estimates. The 2 groups were compared by Student *t* tests. A *p* value <0.05 was considered statistically significant. Data are reported as the mean \pm standard deviation. Data were analyzed for shock versus no shock in relation to sudden death and to selected baseline clinical variables.

RESULTS

Clinical characteristics: The group comprised a total of 39 patients, 35 men (90%) and 4 women (10%), with coronary artery disease and LV ejection fraction <30%. Mean age at the time of AICD implantation was 64 years (range 42 to 79) and was not significantly different within the subgroups of survivors and nonsurvivors. Thirty-three patients (85%) were >60 years old. Indications for AICD implantation included survivors of out-of-hospital cardiac arrest (*n* = 29 [74%]) and recurrent sustained ventricular tachycardia that was symptomatic because of hemodynamic compromise and that was refractory to electrophysiologically guided therapy (*n* = 10 [26%]). Table I lists selective demographic and clinical information for the total group and for subgroups of survivors and nonsurvivors after AICD implantation.

Other surgical techniques: In addition to AICD implantation, 14 patients (36%) had concurrent cardiac surgical procedures, including coronary artery bypass grafting (all 14) and LV aneurysm resection (4 patients). There was no statistical difference in survival or defibrillator discharge between the subgroups of patients who had additional cardiac surgical procedures and the rest of the study patients.

Ventricular function: The LV ejection fraction at the time of AICD implantation was severely depressed among the total study group, with a mean of $21 \pm 4\%$, a median of 21% and a range of 10 to 29%. Table I lists the breakdown of patients by LV ejection fraction in ranges of 26 to 40%, 21 to 25% and <20%, for the total study group, and for subgroups of survivors and nonsurvivors. There was a trend toward lower ejection fractions in nonsurvivors.

TABLE I Clinical Characteristics and Outcome of Study Group

	Total Group	Survivors	Nonsurvivors
No. of pts.	39	30	9
Mean age (range)	64 (41–79)	65 (42–79)	62 (49–72)
Mean LVEF (\pm SD)	21 (\pm 4)	21 (\pm 5)	21 (\pm 3)
LVEF 26–30%	5 (13%)	5 (17%)	0
LVEF 21–25%	15 (38%)	12 (40%)	3 (33%)
LVEF <20%	19 (44%)	13 (43%)	6 (67%)
AICD-terminated arrhythmias (%)	30 (77)	24 (80)	6 (67)
Antiarrhythmic drugs (%)	31 (79)	24 (79)	7 (78)
No drug	8	6	2
Class IA	12	10	2
Class IB	5	4	1
Class IC	2	1	1
Class II	3	3	0
Class III	11	8	3
Amiodarone	9	6	3
Sotalol	2	2	0
Vasodilator drugs (%)	22 (56)	19 (63)	3 (33)
Ca ⁺ antagonists	8	6	2
ACE inhibitors	12	11	1
Nitrates	16	14	2
Digoxin (%)	20 (51)	17 (51)	3 (33)

Percentages refer to percentages of respective subgroups. Mean values and subgroup percentages were not significantly different among subgroups.
ACE = angiotensin-converting enzyme; AICD = automatic implantable cardioverter defibrillator; LVEF = left ventricle ejection fraction; SD = standard deviation.

Hemodynamic data: Hemodynamic data were available for 14 patients at the time of data analysis. Cardiac index in these patients was depressed, at a mean of 2.6 liter/min/m² (2.6 liter/min/m² in survivors and 2.2 liter/min/m² in nonsurvivors). Pulmonary artery wedge pressure was elevated at a mean of 17 mm Hg in the total study group, survivors and nonsurvivors. The small number of patients for whom complete hemodynamic measurements were available did not allow for analysis of the effects of hemodynamic function on survival.

Antiarrhythmic drugs and other pharmacotherapy:

A decision to use antiarrhythmic drugs was based on the frequency and forms of ventricular arrhythmias during continuous electrocardiographic monitoring before hospital discharge. The expected frequency of sustained ventricular arrhythmias based on clinical electrophysiologic observations also supported the decision regarding use of antiarrhythmic agents. At the time of AICD implantation, 31 patients (79%) were discharged while receiving antiarrhythmic therapy, 9 (23%) of whom received amiodarone. The remainder received various antiarrhythmic drugs (Table I). Vasodilator drugs and digoxin were used in 22 (56%) and 20 (51%), respectively, of the patient group, with no statistical difference between survivors and nonsurvivors (Table I).

Relation of automatic implantable cardioverter defibrillator terminated arrhythmia to clinical outcome: All patients were followed until January 31, 1990, with a mean follow-up for survivors of 24.4 months (range 2 to 72). One patient underwent cardiac transplantation 3 months after AICD implantation and was then censored out of the study. Nine patients (23%) died after receiving an AICD, 2 (20%) suddenly. Among the other 7 deaths, 1 was noncardiac (amiodarone pulmonary toxicity) and the others were cardiac (congestive heart failure, electromechanical dissociation and acute myocardial infarction). Among the patients who died, 6 (67%), including 1 sudden death victim, had AICD discharges in the weeks to months before the terminal event.

Among the 30 survivors (77%) in the study, 24 (80%) had AICD discharges. The total potential of sudden death (patients who were shocked or had sudden death and were not previously shocked) was 79%.

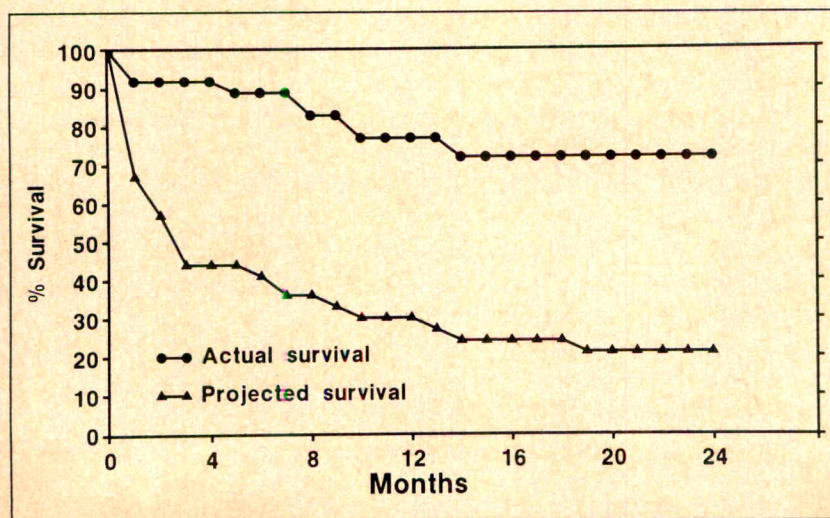


FIGURE 1. Kaplan-Meier corrected actual and projected survival curves for the study group. Projected survival refers to estimated survival of the group had the automatic implantable cardioverter defibrillator not been implanted (see text). The difference between actual and projected survival rates was highly significant ($p < 0.01$) at 1 year and ($p < 0.05$) at 2 years.

Life-table survival analyses: Kaplan-Meier life-table analyses for actual and projected survival are shown in Figure 1. Actuarial survival was 77% at 1 year and 72% at 2 years. The projected survival rate had the AICD not been implanted (patients who survived without an appropriate device discharge) was only 30% at 1 year and 21% at 2 years. The difference between actual and projected survival rates was statistically significant ($p < 0.01$ at 1 year and $p < 0.05$ at 2 years).

DISCUSSION

Previous long-term survival studies in patients with heart failure have demonstrated that patients with coronary artery disease have a worse prognosis than those with other forms of myocardial disease.^{10,11} In a study of patients with severely depressed LV ejection fractions, 80% of deaths were sudden, and patients with coronary artery disease had twice the mortality as those without.¹¹ Moreover, markedly decreased LV ejection fraction^{12,13} and previous episodes of cardiac arrest¹⁴ or drug-refractory ventricular tachycardia adversely affect survival.¹⁵ We therefore studied a group of patients at a particularly high risk of cardiac death. Those with coronary artery disease were survivors of either out-of-hospital cardiac arrest or had drug-refractory, hemodynamically significant ventricular tachycardia, an advanced mean age of 64 years, and a severely depressed LV ejection fraction (mean $21 \pm 4\%$). Any of these characteristics should have independently predicted a high cardiac death rate. Our study group, however, had a remarkably good actuarial survival of 77% at 1 year and 72% at 2 years. The projected survival rate for patients had the AICD not been implanted (patients who survived without an appropriate device discharge) was 30% at 1 year and 21% at 2 years.

The possibility that the group of patients we were studying was less ill than other populations with depressed LV function may limit the general applicability of our findings. Although we did not have New York Heart Association functional classification data on our patients, clearly, in patients with severe depression of LV ejection fraction who were < 60 years, cardiac transplantation would have been considered as an alternative therapy to AICD had congestive heart failure been more advanced. However, among the elderly patients in our study—33 (85%) were > 60 years old—the AICD would have been implanted if indicated, regardless of New York Heart Association functional class. The other demographic characteristics—age, coronary artery disease and previous episodes of survival of lethal ventricular arrhythmias—would have predicted a worse prognosis. Tchou et al⁶ previously reported on the

survival of 25 patients with LV ejection fractions $< 30\%$ who required AICD implantation for lethal arrhythmias. They found an actual survival rate of 87% at a mean follow-up of 552 days. The findings of that smaller study of patients with demographic characteristics similar to those of our patients help to support our findings.

Another confounding influence on our study is the validity of the projected death rates, which were based on AICD discharge experiences. Short of devices with memory or devices that can be monitored during events, the distinction between appropriate and inappropriate shocks can be misleading (see Methods). Furthermore, not all patients who had an appropriate AICD discharge would have died or had recurrent cardiac arrest. Some of the episodes of ventricular tachycardia may have terminated spontaneously or could have been successfully resuscitated in the field had they led to cardiac arrest. Still, the estimated mortality rate does not vary greatly from previous analyses of survival in patients with severely depressed LV ejection fraction.^{12,16,17} In either event, the estimated survival rate does not detract from the unexpected and high survival of our total group.

In conclusion, our study strongly suggests that the AICD is beneficial in improving survival in patients with coronary artery disease and lethal arrhythmias, despite severely depressed LV function.

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Comparison of Intravascular Ultrasound, External Ultrasound and Digital Angiography for Evaluation of Peripheral Artery Dimensions and Morphology

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Validation of catheter-based intravascular ultrasound imaging has been based on comparisons with histology and digital angiography, each of which may have limitations in the assessment of arterial size and morphology. External, high-frequency ultrasound can accurately determine vessel dimensions and morphology and because, like intravascular ultrasound, it also provides cross-sectional arterial ultrasound images, it may be a more appropriate technique for the in vivo comparison of arterial dimensions and morphology determined by intravascular ultrasound.

Thus, intravascular ultrasound, external 2-dimensional ultrasound, Doppler color-flow imaging and digital angiography were compared for assessment of arterial dimensions and wall morphology at 29 femoral artery sites in 15 patients. Intravascular ultrasound and the other 3 imaging modalities correlated well in determination of lumen diameter (2-dimensional, $r = 0.98$, standard error of the estimate [SEE] = 0.14; Doppler color flow, $r = 0.91$, SEE = 1.11; angiography, $r = 0.95$, SEE = 0.91) and cross-sectional area (2-dimensional, $r = 0.97$, SEE = 0.04; Doppler color flow, $r = 0.92$, SEE = 0.14; angiography, $r = 0.96$, SEE = 0.08). However, lumen size measured by Doppler color flow was consistently smaller than that measured by the other 3 imaging modalities. Intravascular ultrasound detected arterial plaque at 15 sites, 5 of which were hypoechoic (soft) and 10 hyper-echoic with distal shadowing (hard). Plaque was

identified at 12 of 15 sites by 2-dimensional imaging ($p = 0.30$ vs intravascular ultrasound), but at only 6 of 15 sites by angiography ($p = 0.003$ vs intravascular ultrasound), only 1 of which was thought to be calcified plaque. These data indicate that arterial dimensions determined by intravascular ultrasound correlate well with both external ultrasound and angiography in normal and minimally diseased peripheral arteries. Doppler color flow underestimates true lumen size. Angiography is often discordant with both intravascular and external ultrasound in determining the presence and composition of arterial plaque.

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Catheter-based intravascular ultrasound imaging is an exciting new vascular imaging technique. However, before clinical application, the technique requires validation. In vitro determinations of vessel size and morphology by intravascular ultrasound correlate well with histology.¹⁻⁵ Arterial dimensions determined by intravascular ultrasound in vivo correlate well with angiography.⁶⁻⁸ However, intravascular ultrasound and angiography are often discordant in the assessment of vessel morphology.^{6,7,9} Whether this is because intravascular ultrasound is more sensitive for evaluating vessel morphology than angiography, or whether interpretations of intravascular ultrasound images are not representative of true vessel morphology, remains uncertain.

External ultrasound imaging using both 2-dimensional and Doppler modalities is a well-validated technique for assessment of the peripheral vascular system.¹⁰⁻¹⁵ Furthermore, rather than comparing intravascular ultrasound images with the silhouette images produced by contrast angiography, a more appropriate comparison of intravascular ultrasound, particularly for

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evaluation of vessel morphology, would be with external ultrasound, which provides similar types of vascular images. Agreement between intravascular and external ultrasound would be further evidence supporting the accuracy of intravascular ultrasound for determination of vessel size and morphology. Therefore, the purpose of this study was to compare intravascular ultrasound with external 2-dimensional ultrasound, Doppler color-flow imaging and digital angiography in the assessment of peripheral vascular size and morphology in a group of patients for whom all 4 imaging modalities were used.

METHODS

Patients: We examined 15 patients (10 men, mean age \pm standard deviation 56 ± 19 years [range 24 to 75]), none of whom had a history of peripheral artery disease. All were undergoing diagnostic cardiac catheterization for suspected coronary, valvular or congenital heart disease, and all agreed to a protocol approved by the institutional review board permitting peripheral artery imaging in conjunction with the cardiac catheterization procedure.

External ultrasound: External ultrasound images were obtained after the patient was brought to the catheterization laboratory. A total of 29 sites from the common and superficial femoral arteries contralateral to the arterial puncture site were examined. External images were obtained with an Acuson 128 system (Mountain View, California) using a 7.5-MHz linear array transducer. After long-axis imaging to identify the femoral artery, transverse axis views of the artery were obtained. Depth and sector settings were set to the minimal levels permitting display of the entire arterial lumen. Gain settings were set to levels optimizing the lumen/arterial wall interface. Only images providing high-quality definition of the arterial lumen and vessel edges were used (Figure 1A). System resolution in both axial and lateral planes for arterial images obtained in this manner has been reported to be approximately 1 mm.¹⁶

Images were recorded on high-fidelity videotape for off-line analysis. The frame in which the arterial lumen was at its maximal diameter was frozen, then analyzed off-line for vessel dimensions and morphology. Each patient provided from 1 to 5 image sites per examina-

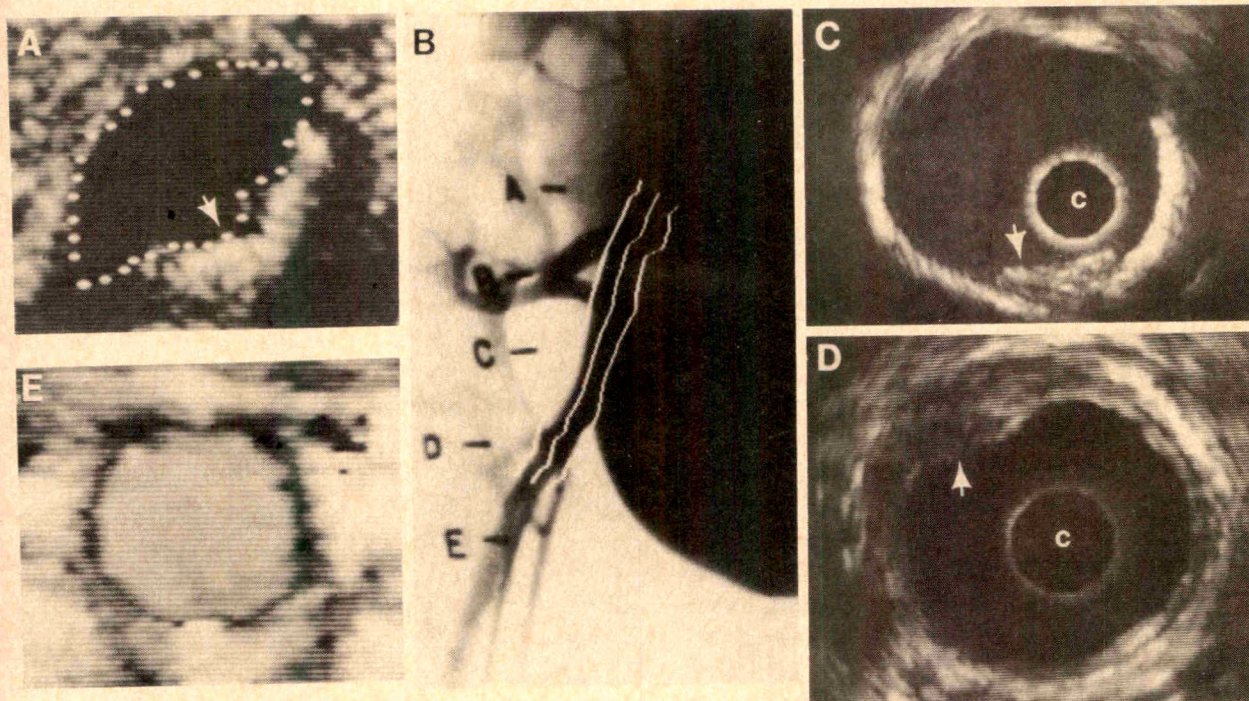


FIGURE 1. Representative images from all vascular imaging modalities. Clockwise from upper left: **A**, 2-dimensional external ultrasound image of site marked "A" on the angiogram (**B**). The arterial lumen is echo-free, and is outlined by the dotted line to determine luminal cross-sectional area. Arrow, hard plaque demonstrating hyperechoicity and acoustic shadowing. **B**, digital angiogram of the right common femoral artery. Imaging points "A through E" indicate surface radiopaque markers. **C**, intravascular ultrasound image from site "C" on the angiogram (**B**). Arrow, hard plaque demonstrating hyperechoicity and acoustic shadowing. Catheter blank spot (c) is within the echo-free arterial lumen. **D**, intravascular ultrasound image taken from site "D" on the angiogram (**B**). Arrow indicates soft plaque. **E**, Doppler color-flow external ultrasound image of site "E" on the angiogram (**B**). Shaded area, representing the color Doppler signal, is the vessel lumen.

tion. Radiopaque markers were placed on the skin surface to correlate external ultrasound imaging sites with angiography and intravascular ultrasound (Figure 1B).

After external 2-dimensional imaging, Doppler color-flow imaging (Figure 1E) was performed at the same site using velocity-variance maps. Color gains and velocity limits were adjusted to obtain maximal lumen color, without a color signal overlying tissue. Reject was set to minimal levels. Angle-directed color Doppler optimization was performed to produce the largest color jet possible within the vessel lumen. The color Doppler signal was superimposed on the previously frozen anatomic image for off-line dimension analysis.

Image analysis was performed while blinded to results of angiography and intravascular ultrasound. A commercially available digitizing pad, computer and software were used (Nova Microsonics, Mahwah, New Jersey). Two-dimensional images were examined for the occurrence of arterial plaque. The character of the plaque as either hypoechoic (soft) or hyperechoic with distal shadowing (hard) was noted.² Arterial lumen diameter was measured in the transverse plane of the vessel cross section. Lumen area was planimeted by tracing the entire lumen boundary with the arterial wall. For the Doppler color-flow image, the maximal transverse diameter of the color Doppler signal within the arterial cross section was measured. The complete color Doppler signal was planimeted for assessment of cross-sectional area.

Intravascular ultrasound: Arterial access was secured with an 8Fr sheath, usually in the right femoral artery. An 8Fr Judkins right coronary artery guiding catheter was then positioned, either with or without the assistance of a guidewire in the contralateral femoral system. A commercially available intravascular ultrasound system, consisting of a blunt-tipped 6Fr sheath containing a metal core with a single 20-MHz piezoelectric crystal bonded to the tip, and mechanically rotated at 900 rpm (BSC-Diasonics, Watertown, Massachusetts), was then positioned through the guiding catheter at the previously marked sites to obtain intravascular ultrasound images (Figure 1, C and D). The position of the intravascular ultrasound catheter was also recorded on cine film for subsequent determination of vessel dimensions by digital angiography. Images were analyzed for arterial plaque and dimensions in the same manner as external 2-dimensional ultrasound images. System axial and lateral resolution tested in our laboratory at a 5.0-mm radial beam distance are 0.4 and 1.3 mm, respectively.

Digital subtraction angiography: A digital subtraction angiogram of the femoral artery was then obtained

by the injection, by hand, of nonionic contrast through the guiding catheter (Figure 1B). Images were recorded with an ADAC 4100-C system, interfaced to a General Electric-MPX L/U x-ray unit. Single-plane anterior-posterior view images were acquired with use of a 9-inch image intensifier and fed into a $512 \times 512 \times 8$ pixel matrix at 30 frames/s. All areas of interest were centered to avoid pin-cushion distortion. R-wave-gated masked mode subtraction was performed after the procedure. All images were acquired and stored in digital format.

Images were analyzed while blinded to results of ultrasound imaging with a previously validated, commercially available software program.^{17,18} A grid placed at the level of the artery was used for calibration. Absolute minimal luminal diameter, cross-sectional area and the presence of plaque in the region of the radiopaque markers and precisely at the previously recorded intravascular ultrasound catheter site were examined. Each site of plaque was further characterized as either containing or not containing calcium, to correspond potentially with the respective ultrasound designations of hard and soft plaque, as previously defined.²

Data analysis: Correlation of vessel dimensions between imaging techniques were by linear regression analysis. R values represent Pearson correlation coefficients. Discrete variables were compared by the chi-square test, with Yates' correction.

RESULTS

As shown in Figures 2 and 3, vessel diameters and cross-sectional areas measured by intravascular ultrasound correlated closely with those measured by external 2-dimensional imaging, Doppler color-flow imaging and digital subtraction angiography (all $r > 0.90$). Whereas arterial dimensions determined by intravascular ultrasound were linearly related to those determined by both external 2-dimensional imaging and digital subtraction angiography, dimensions determined by Doppler color-flow imaging tended to underestimate those determined by intravascular ultrasound, as indicated by the slope of the regression line > 1.0 and the y intercept > 0 for both diameter and cross-sectional area measurements.

Intravascular ultrasound detected 15 sites of plaque of the total 29 sites examined. In all cases, the plaque resulted in $< 50\%$ luminal diameter narrowing on intravascular ultrasound cross-sectional images. As shown in Figure 4, external 2-dimensional ultrasound imaging identified 12 of these 15 plaque sites (chi-square = 1.48, $p = 0.30$ vs intravascular ultrasound). After plaque composition was distinguished as having either a

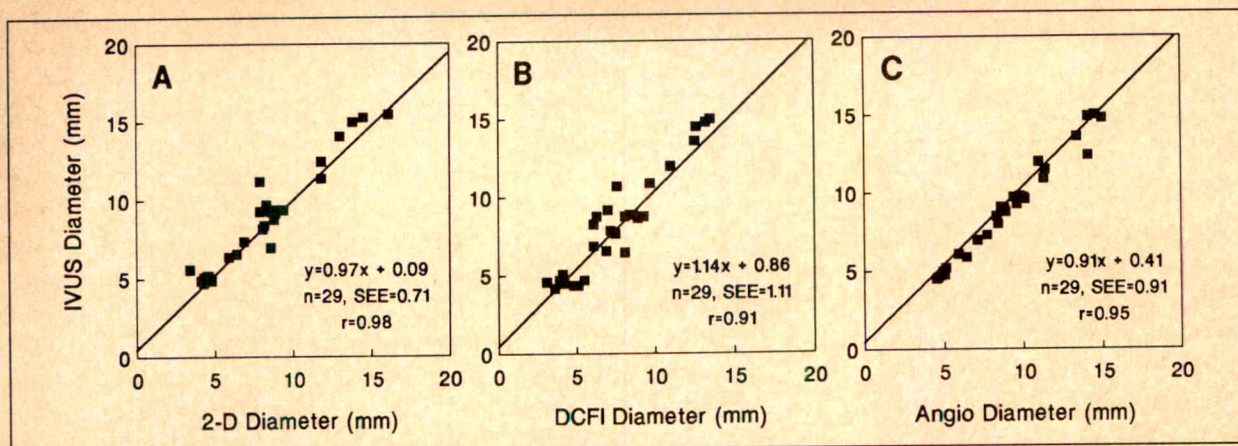


FIGURE 2. Linear regression equations and correlation of arterial lumen diameters measured by intravascular ultrasound (IVUS) and (A) 2-dimensional (2-D) external ultrasound, (B) Doppler color-flow imaging (DCFI), and (C) digital angiography (Angio). Individual data points are shown, as are regression equations, Pearson correlation coefficients (r), and standard error of the estimate (SEE) for each equation.

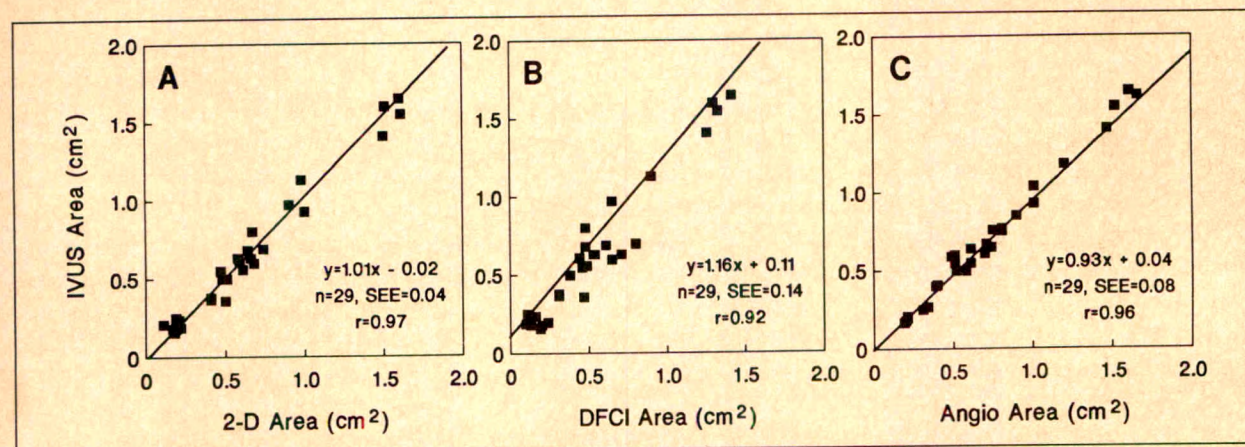


FIGURE 3. Linear regression equations and correlation of arterial lumen areas measured by intravascular ultrasound and (A) 2-dimensional external ultrasound, (B) Doppler color-flow imaging, and (C) digital angiography. Individual data points are shown, as are regression equations, Pearson correlation coefficients (r), and standard error of the estimate for each equation. Abbreviations as in Figure 2.

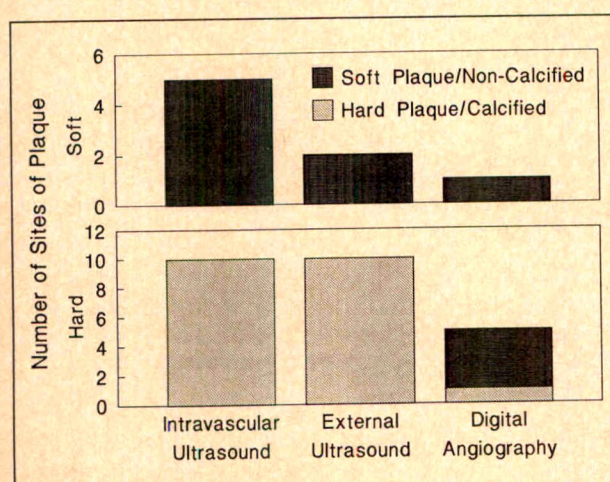


FIGURE 4. Relation of the presence and character of plaque detected by intravascular ultrasound to that determined by 2-dimensional external ultrasound and digital angiography. Plaque sites are distinguished by hard and soft plaque, as identified by intravascular ultrasound.

soft or hard appearance by intravascular ultrasound, all 10 hard plaque sites were detected and characterized as having a hard appearance by external 2-dimensional imaging. Of the 5 plaque sites determined to have a soft appearance by intravascular ultrasound, only 2 were detected by external 2-dimensional imaging, and both were characterized as soft. In no instance was plaque noted by external ultrasound and not by intravascular ultrasound.

As also shown in Figure 4, angiography identified only 6 of 15 sites of plaque noted by intravascular ultrasound (chi-square = 10.16, $p = 0.003$ vs intravascular ultrasound). In all cases, the sites of plaque caused only minor irregularities of the angiographic lumen. When distinguished by plaque composition, only 5 of the 10 sites of hard plaque noted by intravascular ultrasound were detected by angiography, and only 1 was thought to be calcified. The 1 site of soft plaque noted

by intravascular ultrasound that had also been detected by angiography was not felt to be calcified on angiography. In no instance was plaque noted by angiography and not by intravascular ultrasound.

DISCUSSION

Arterial dimensions: These data indicate that in normal and minimally diseased segments, peripheral artery dimensions determined by intravascular ultrasound correlate well not only with angiography, as has previously been shown,⁶⁻⁸ but also with dimensions determined by both external 2-dimensional ultrasound and Doppler color-flow imaging. The correlation with 2-dimensional ultrasound imaging is a particularly important observation. Angiography and ultrasound are entirely dissimilar imaging modalities. Whereas angiography provides a projectional, static image of the vessel of interest, usually in longitudinal views, intravascular ultrasound provides a real-time cross-sectional image. Given the dissimilarities between the 2 techniques, it is somewhat surprising that angiography and intravascular ultrasound agreed as well as they did.

Pandian et al³ previously demonstrated *in vitro* that external ultrasound and intravascular ultrasound yield similar measurements of arterial dimensions.³ This study extends those observations to the human *in vivo* setting by showing that whether the ultrasound image is acquired from a transducer external to the artery, or from within the artery, the arterial dimensions are similar. In conjunction with the good correlations with angiographically determined arterial dimensions, such data would further support the validity of intravascular ultrasound for determination of human arterial dimensions.

Doppler angiography: These data also provided us with the ability to assess the use of the color Doppler signal generated by arterial blood flow to produce a Doppler angiogram, or "angiodynography."¹² It has been proposed that when the color Doppler signal is used to represent the blood flow within the vessel lumen, the lumen thus outlined accurately represents the true vessel lumen.¹²

That this is indeed not the case is supported by our observation that, although arterial dimensions measured by intravascular ultrasound and Doppler color-flow imaging are well correlated, the arterial lumen outlined by the color Doppler signal tends to be systematically smaller than that determined by intravascular ultrasound. Similar results were noted when dimensions determined by Doppler color flow were compared with external 2-dimensional ultrasound measurements as well as with digital angiographic measure-

ments. This is not to say that Doppler color-flow imaging is not a valuable component of the noninvasive ultrasound examination of the peripheral artery system. Doppler color-flow imaging assists in vessel identification and recognition, identification of areas of disordered flow, more accurate spectral Doppler interrogation, and generally permits an easier and more rapid peripheral artery ultrasound examination.¹¹ However, the color Doppler signal depends on the character of blood flow in terms of velocity, direction and associated turbulence, the angle of the Doppler beam with respect to flow, image and Doppler gain settings, and computer averaging techniques. The influence of these variables on the color Doppler signal results in a signal that typically underestimates arterial lumen size, and thus should not be used to determine arterial dimensions.

Arterial morphology: The most noteworthy finding of this study is that sites of plaque noted by both intravascular and external ultrasound imaging are often not identified by angiography. We^{6,8} and others^{19,20} have previously noted discordance between the angiogram and intravascular ultrasound in determination of vessel wall morphology. Whether this was a result of artifacts of intravascular ultrasound imaging, errors of the angiogram, or a combination of both, has been a matter of uncertainty. That intravascular and external ultrasound correlated closely in the detection of plaque sites would indicate that the areas of plaque revealed by intravascular ultrasound are likely not artifacts, but true sites of plaque that are beyond the resolution of the angiogram. These *in vivo* data would support pathologic data that indicate that ultrasound imaging correlates closely with histology in identifying arterial plaque,^{1-5,21} whereas angiography correlates poorly with histology in identifying arterial plaque.²²⁻²⁴ The angiogram appears to be especially poor at identifying plaque if the areas of plaque cause noncritical vascular narrowing, as in this study, or are distributed in a concentric manner.^{22,23}

Angiography also did not correlate well with either intravascular or external ultrasound in the determination of plaque composition. Only 1 of 10 areas of hard plaque identified by ultrasound was thought to be calcified angiographically. Whether this is because of the insensitivity of angiography in detecting calcification, or the erroneous equation of hard plaque noted by intravascular ultrasound with the occurrence of tissue calcification, requires further histologic confirmation. It appears that echogenic areas of plaque with acoustic shadowing noted by both intravascular^{2,4,5} and external ultrasound²¹ may be a result of either calcification or fibrosis, or both. That the angiogram may be relatively

insensitive in its ability to characterize plaque composition may have important clinical implications. This may be especially relevant if the use of a particular interventional device, such as atherectomy, laser or ultrasonic ablation, is directed more toward a particular type of plaque (i.e., calcified), as has been suggested.^{25,26}

Study limitations: The excellent correlation of intravascular ultrasound, external ultrasound and angiography for assessment of vessel dimensions in normal and minimally diseased arteries likely does not extend to more severely diseased arteries. Assumption of lumen eccentricity with more extensive disease results in limitations of both single-plane angiography and ultrasound in the accurate characterization of vessel geometry and size. Recognition of this limitation does not, however, detract from the primary findings of this study: Under ideal circumstances intravascular ultrasound can accurately determine vessel dimensions and geometry, and vessel morphology characterized by intravascular ultrasound is similar to morphologic assessments by external ultrasound.

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Left Ventricular Diastolic Function in Patients with Left Ventricular Systolic Dysfunction Due to Coronary Artery Disease and Effect of Nicardipine

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To assess the effect of nicardipine on left ventricular (LV) diastolic function independent of concurrent effects on loading conditions in patients with LV systolic dysfunction due to coronary artery disease, equihypotensive doses of intravenous nitroprusside and nicardipine were administered to 12 patients with congestive heart failure due to previous myocardial infarction (LV ejection fraction <0.40). LV micromanometer pressure and simultaneous radionuclide volume were obtained during a baseline period, during nitroprusside infusion, during a second baseline period and during nicardipine infusion. Mean systemic arterial pressure decreased an average of 21 mm Hg with nitroprusside and 19 mm Hg with nicardipine. A greater decrease in LV end-diastolic pressure was observed with nitroprusside (29 ± 2 to 15 ± 2 mm Hg, $p < 0.01$) than with nicardipine (29 ± 2 to 25 ± 3 mm Hg, $p < 0.05$). There was a decrease in the time constant of relaxation during nitroprusside but not during nicardipine infusion. There was enough overlap in LV volumes in the baseline and nitroprusside periods to compare diastolic pressure-volume relations over a common range of volumes in 4 patients, and enough overlap in the baseline and nicardipine periods in 11 patients.

The relation was shifted downward in 3 of 4 patients taking nitroprusside and in 6 of 11 patients taking nicardipine. The relation between end-diastolic pressure and volume was not shifted with nicardipine. Thus, in patients with LV systolic dysfunction due to coronary artery disease, nicardipine shifted the diastolic pressure-volume relation downward in some patients, but did not alter the relation between end-diastolic pressure and volume, and, unlike nitroprusside, did not increase the rate of isovolumic relaxation. With regard to acute effects on diastolic function, nicardipine did not offer an advantage over nitroprusside in this patient group.

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Abnormalities of diastolic left ventricular (LV) function have been described in patients with heart failure associated with systolic dysfunction,¹⁻³ and may contribute independently to elevated atrial pressures in this condition. Calcium antagonists improve diastolic function in some patients with coronary artery disease and normal systolic function.^{4,5} Therefore, it is possible that calcium antagonists would have a beneficial effect on diastolic function in patients with LV systolic dysfunction due to previous myocardial infarction. The new dihydropyridine calcium antagonist nicardipine is a powerful coronary vasodilator.⁶ Some studies have suggested that nicardipine improves diastolic function in patients with coronary artery disease,⁷ including those with mild to moderate LV systolic dysfunction.⁸ Since "pure" vasodilators such as nitroprusside may favorably influence indexes of diastolic function, even in the absence of direct effects on diastolic properties of the myocardium,^{3,9-11} we compared the effects of nicardipine on diastolic function with those of equihypotensive doses of nitroprusside in patients with LV systolic dysfunction resulting from coronary artery disease.

From the Cardiac Unit, Department of Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts. This study was performed during Dr. Aroney's tenure as an Overseas Clinical Fellow of the National Heart Foundation of Australia, Canberra, ACT, Australia, and Dr. Fifer's tenure as a Clinician-Scientist of the American Heart Association, Dallas, Texas. This study was supported in part by funds from Syntex Research, Palo Alto, California. Manuscript received October 16, 1990; revised manuscript received and accepted December 17, 1990.

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METHODS

Patients: The study group comprised 11 men and 1 woman (mean age \pm standard error of the mean 64 ± 2 years) with LV systolic dysfunction (radionuclide ejection fraction <0.40) due to coronary artery disease. Five patients were in New York Heart Association class II, 2 were in class III and 5 were in class IV. All patients were in sinus rhythm. Nine patients were taking digoxin, 11 diuretic drugs, 7 captopril or enalapril, 11 long-acting nitrates, 3 diltiazem and 2 antiarrhythmic agents. Informed consent was obtained from all patients.

Hemodynamic measurements: Patients underwent left- and right-sided cardiac catheterization without premedication 8 to 24 hours after discontinuation of all cardiac medications except antiarrhythmic agents. Left-sided cardiac catheterization was performed from the femoral approach using a micromanometer catheter (Millar) in 11 patients and a fluid-filled catheter in 1 patient. Systemic arterial pressure was measured from the sidearm of a femoral artery introducer. The following hemodynamic variables were recorded: heart rate, right atrial pressure, pulmonary artery wedge pressure, high-fidelity LV pressure, mean systemic arterial pressure and (in 11 patients) the first derivative of LV pressure (dP/dt) (by electronic differentiation). Cardiac index and systemic and pulmonary vascular resistances were calculated from cardiac output obtained by the thermodilution technique.

Hemodynamic and radionuclide data were obtained at baseline, with nitroprusside infused at an initial dosage of $25 \mu\text{g}/\text{min}$ and titrated upward to achieve a 20-mm Hg decrease in mean systemic arterial pressure, 15 minutes after discontinuation of nitroprusside, and with nicardipine infused at an initial dosage of $1 \text{ mg}/\text{min}$ to achieve a 20-mm Hg reduction in mean arterial pressure ("bolus") and titrated downward to maintain this reduction over a 10-minute period ("infusion").

Gated blood pool imaging: LV volume was calculated from supine gated blood pool images as previously described.³ Briefly, scans were acquired in the anterior (16 frames) and left anterior oblique (32 frames) views after labeling of red blood cells in vivo with 30 mCi of technetium-99m. With use of the left anterior oblique view, a time-activity curve of the left ventricle was constructed by a semiautomated edge-detection method with a variable region of interest. During nitroprusside infusion, the second baseline period and nicardipine infusion images were acquired in only the left anterior oblique view, and care was taken to avoid patient and camera movement during the study. Absolute LV end-diastolic volume at baseline was derived by a geometric biplane area-length method. Volumes at other time

points in the cardiac cycle and in the nitroprusside infusion, second baseline, and nicardipine infusion periods were calculated as the baseline end-diastolic volume multiplied by the ratio of counts in a particular frame to counts in the baseline end-diastolic frame. Counts were smoothed using a 3-point weighted moving average (coefficients: 0.25, 0.50 and 0.25). Counts in scans obtained during nitroprusside infusion, second baseline and nicardipine infusion were corrected for differences from the baseline scan in acquisition time and frame interval and for physical and biologic decay of the isotope.

Data analysis: In the 11 patients with high-fidelity LV pressure measurements, tracings from 4 consecutive beats at the midpoint of the gated scan acquisition were digitized on a Summagraphics Bitpad interfaced to a VAX 780 computer. Diastolic pressure-volume curves were constructed by plotting these pressures with the radionuclide ventriculographic volumes measured at the same intervals from the peak of the R wave of the electrocardiogram. A change in overall LV distensibility during infusion of nitroprusside or nicardipine compared with baseline was defined as an LV pressure difference ≥ 3 mm Hg in the passive filling portion of the diastolic pressure-volume relation.

The time constant of LV isovolumic relaxation using the logarithmic method (T_L) was obtained in 11 patients from micromanometer LV pressure. T_L was defined as the negative reciprocal of the slope of the linear fit of the natural logarithm of LV pressure (from diastolic notch pressure to the pressure of the simultaneous v wave of the pulmonary artery wedge tracing) versus time.¹² In 10 patients with technically adequate data, the time constant (T_D) was also calculated as the negative reciprocal of dP/dt versus LV pressure over the same interval.¹³

Statistics: Results are expressed as mean \pm standard error of the mean. Comparisons between 2 measurements were obtained by paired t test. The 4 treatment periods were compared by analysis of variance, with differences between group means assessed by the Newman-Keuls test. Differences for which $p < 0.05$ were considered significant.

RESULTS

Hemodynamic responses to nitroprusside and nicardipine (Table I): During nitroprusside infusion ($59 \pm 11 \mu\text{g}/\text{min}$), mean systemic arterial, right atrial, pulmonary artery and LV end-diastolic pressures decreased, as did LV end-systolic and end-diastolic volumes. There was no significant change in heart rate or cardiac index. Nicardipine administration (bolus dose $1.6 \pm 0.2 \text{ mg}$, infusion rate $0.26 \pm 0.02 \text{ mg}/\text{min}$, total

dose 4.8 ± 0.3 mg) caused a decrease in mean systemic arterial pressure. Heart rate was not affected. There was no change in right atrial or pulmonary artery wedge pressures, although LV end-diastolic pressure decreased slightly. Cardiac index increased. LV end-

systolic volume decreased, whereas end-diastolic volume did not change.

Comparison of the effects of nicardipine with those of nitroprusside showed a similar decrease in mean systemic arterial pressure with the 2 drugs. LV end-systol-

TABLE I Effects of Nitroprusside and Nicardipine on Hemodynamics and Indexes of Relaxation

Pt. No.	Condition	HR	CI	MAP	RAP	PCWP	LVEDP	LVEDV	LVESV	peak - dP/dt	T _L	T _D
1	Baseline	83	2.13	82	4	19	28	400	320	1,113	61	101
	Nitroprusside	77	1.99	64	3	8	9	367	296	844	43	85
	Baseline	96	1.77	77	6	22	29	400	305	1,000	66	111
	Nicardipine	88	2.15	66	7	23	25	400	312	915	72	76
2	Baseline	110	1.84	87	11	37	35	568	515	800	91	
	Nitroprusside	108	3.53	69	4	22	23	522	457	680	80	
	Baseline	105	1.89	88	12	35	34	564	507	780	93	
	Nicardipine	105	3.18	66	10	26	27	582	501	790	73	
3	Baseline	82	2.19	102	1	13	23	440	348			
	Nitroprusside	87	2.14	71	0	1	2	345	268			
	Baseline	80	2.42	92	2	14	22	422	345			
	Nicardipine	79	3.02	60	2	5	6	400	303			
4	Baseline	84	1.89	73	1	15	24	352	314	800	66	90
	Nitroprusside	82	1.76	57	0	8	13	315	291	700	57	81
	Baseline	80	1.80	76	3	28	28	355	317	750	111	99
	Nicardipine	80	1.95	65	3	30	28	353	303	600	119	97
5	Baseline	72	2.46	80	4	18	28	405	357	1,000	68	100
	Nitroprusside	72	2.39	72	3	6	17	362	302	950	44	72
	Baseline	69	2.27	81	4	27	30	405	345	950	68	113
	Nicardipine	71	3.16	70	6	23	27	387	321	900	60	89
6	Baseline	84	1.65	85	8	34	34	363	295	975	92	141
	Nitroprusside	85	2.33	72	2	15	20	349	286	941	52	82
	Baseline	82	1.80	85	8	35	36	363	300	993	85	125
	Nicardipine	88	2.09	72	10	39	35	354	296	865	102	89
7	Baseline	83	1.94	88	8	32	35	427	344	975	87	128
	Nitroprusside	84	2.21	80	6	25	28	435	341	950	85	95
	Baseline	84	1.48	102	9	35	45	460	366	1,000	76	101
	Nicardipine	84	2.20	88	8	37	42	458	365	850	79	124
8	Baseline	90	2.10	135	1	28	25	264	221	1,614	55	166
	Nitroprusside	90	2.10	90	0	2	5	204	178	1,410	32	63
	Baseline	88	2.00	129	1	14	25	250	210	1,310	59	80
	Nicardipine	90	2.60	80	0	7	12	231	188	1,290	57	55
9	Baseline	100	1.26	88	13	38	32	404	365	825	88	89
	Nitroprusside	100	1.55	75	15	29	27	404	351	664	84	89
	Baseline	100	1.19	84	14	41	35	393	351	780	90	139
	Nicardipine	97	1.57	71	15	34	32	394	341	610	111	106
10	Baseline	75	1.83	105	6	11	13	357	262	1,490	45	97
	Nitroprusside	75	1.83	84	5	6	8	300	217	1,380	35	76
	Baseline	74	1.76	100	5	10	12	360	273	1,430	50	77
	Nicardipine	74	2.75	85	7	13	15	345	237	1,410	46	76
11	Baseline	91	1.15	89	6	36	34	431	390	990	65	120
	Nitroprusside	89	1.34	73	3	14	15	405	365	830	48	86
	Baseline	80	1.18	83	6	29	32	425	383	810	64	124
	Nicardipine	80	1.86	67	0	28	33	427	366	800	55	101
12	Baseline	91	1.63	113	11	27	31	406	374	1,010	73	104
	Nitroprusside	53	1.21	70	4	7	12	392	351	820	55	103
	Baseline	85	1.42	94	12	16	25	410	363	910	73	102
	Nicardipine	65	1.92	71	10	13	22	400	362	890	55	110
Mean ± SEM	Baseline	87	1.84	94	6	26	29	401	342	1,054	72	114
	Nitroprusside	84	2.03	73	4	12	15	367	309	924	56	83
	Baseline	85	1.75	91	6	26	29	401	339	974	76	107
	Nicardipine	83	2.37	72	7	23	25	395	325	902	75	92
		± 3*	± 0.16*†	± 2*	± 1†	± 3†	± 3*†	± 24†	± 22*†	± 75*	± 7†	± 6

* p < 0.05 versus preceding baseline; † p < 0.05 versus nitroprusside.

Values shown are mean values ± standard error of the mean.

CI = cardiac index (liters/min/m²); HR = heart rate (beats/min); LVEDP = left ventricular end-diastolic pressure (mm Hg); LVEDV = left ventricular end-diastolic volume (ml); LVESV = left ventricular end-systolic volume (ml); Peak - dP/dt = peak negative first derivative of left ventricular pressure (mm Hg/s); MAP = mean systemic arterial pressure (mm Hg); PCWP = pulmonary artery wedge pressure (mm Hg); RAP = right atrial pressure (mm Hg); SEM = standard error of the mean; T_L = time constant of isovolumic relaxation using logarithmic derivative method (ms); T_D = time constant of isovolumic relaxation using logarithmic method (ms).

ic volume was reduced to a greater extent by nitroprusside than by nicardipine. LV preload, assessed by both end-diastolic pressure and end-diastolic volume, was reduced to a much greater extent by nitroprusside than by nicardipine.

Isovolumic relaxation (Table I): Peak negative LV dP/dt decreased with both nitroprusside and nicardipine. With nitroprusside, there were decreases in T_L and T_D ; these did not change significantly with nicardipine.

Diastolic pressure-volume relation: Eleven of the study patients had complete pressure and volume data. Seven of these 11 had decreases in LV volume with nitroprusside that separated the baseline and nitroprusside pressure-volume curves enough to prevent comparison over a common range of volume. Of the 4 patients with sufficient overlap of the curves to allow comparison, nitroprusside caused a downward shift in the diastolic pressure-volume relation, indicating improved LV distensibility, in 3 (Figure 1). Comparison of the diastolic pressure-volume relation at baseline and with nicardipine was possible in 11 patients. Nicardipine

caused a downward shift in the diastolic pressure-volume relation in 6 of the 11 patients (Figure 2). To assess the effect of right-sided cardiac pressures on the LV diastolic pressure-volume relation, concomitant changes in right atrial pressure were noted. The presence or absence of downward shifts with nitroprusside and nicardipine did not correlate with changes in right atrial pressure during drug administration.

Mean end-diastolic pressure and volume for the 12 patients during the 4 treatment periods are plotted in Figure 3. Visual inspection of these data indicates that nicardipine did not cause a significant shift in the relation between end-diastolic pressure and volume away from that observed for the 2 baseline and nitroprusside periods; this conclusion is corroborated by an exponential curve fit to the baseline and nitroprusside points.

DISCUSSION

We have previously reported the effects of nicardipine on systolic function in a larger group of patients with LV systolic dysfunction that included the present study group.¹⁴ We found that nicardipine shifted the

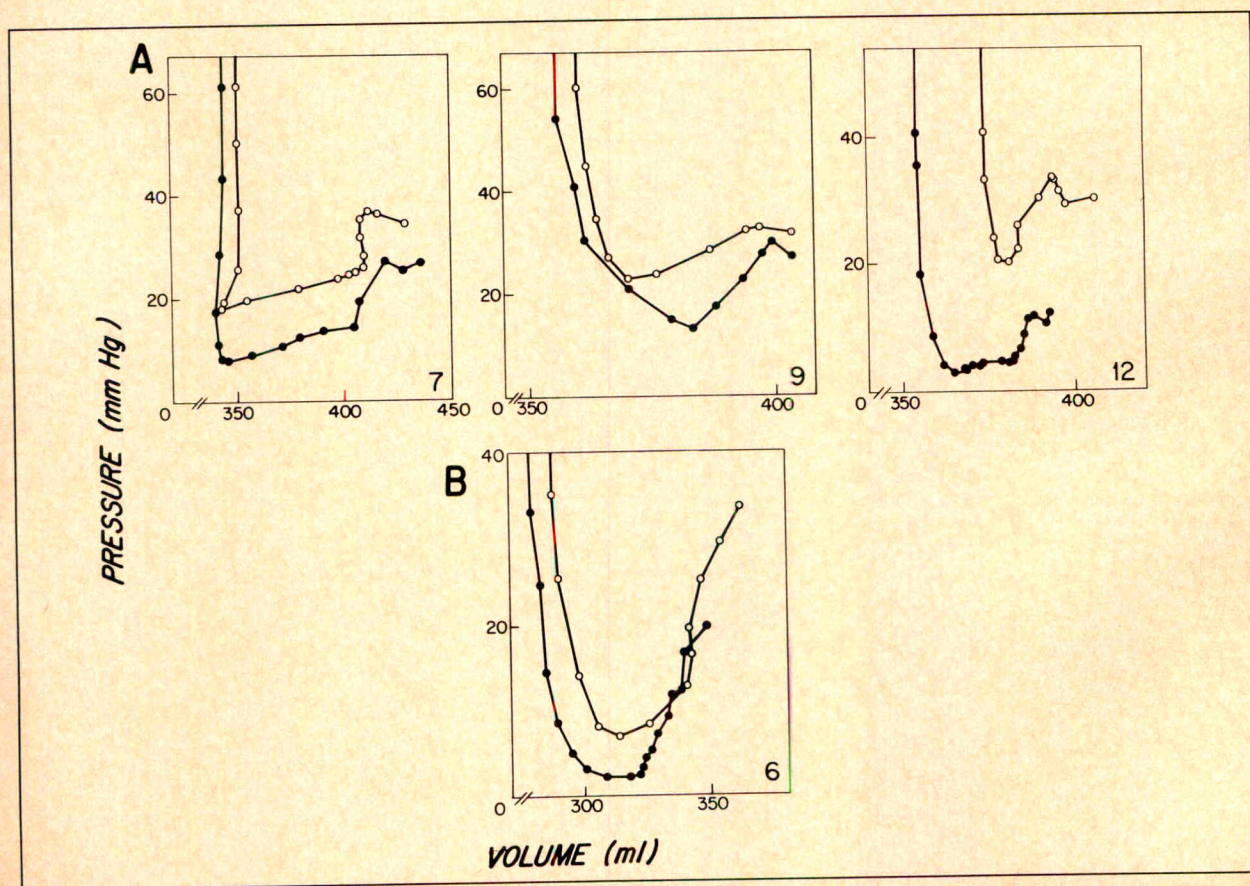


FIGURE 1. Left ventricular diastolic pressure-volume relations during the first baseline period (open circles) and during administration of nitroprusside (closed circles). Overlap between baseline and nitroprusside curves sufficient to allow comparison of the curves over a common range of volume was present in 4 patients. Three patients (A) had a downward shift of the diastolic pressure-volume relation, defined as a pressure difference of ≥ 3 mm Hg during the passive filling portion of the relation. One patient (B) had a diastolic pressure-volume relation that was not shifted. Patient numbers are indicated in the lower right-hand corner of graphs.

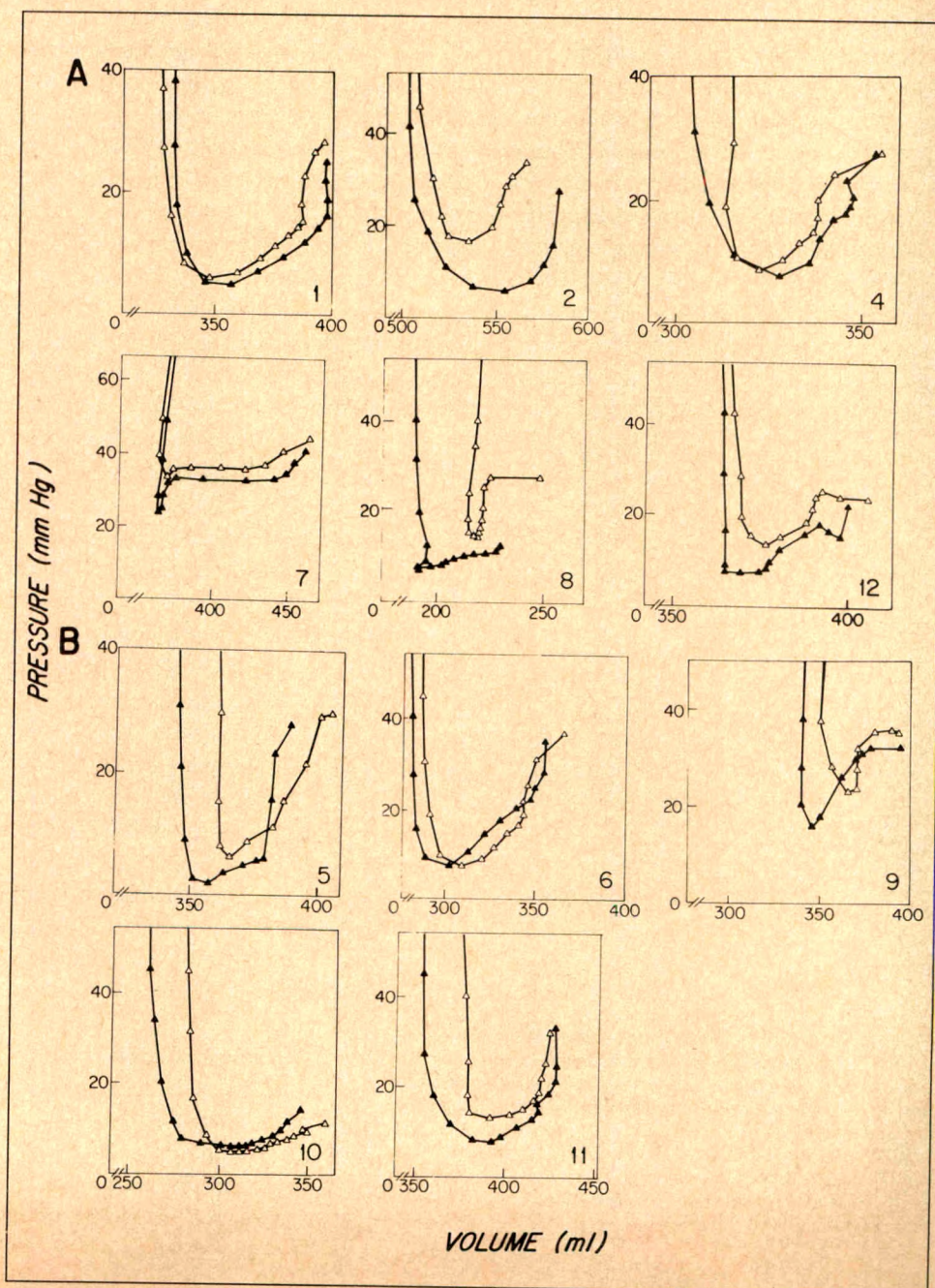
LV end-systolic pressure-volume relation rightward, indicating a negative inotropic effect, in 12 of 14 patients. Despite this effect, there was an overall improvement in pump performance of the left ventricle due at least in large part to afterload reduction. To assess the direct effects of nicardipine on diastolic properties of the LV myocardium, we attempted to account for nonspecific influences of nicardipine mediated by load reduction by comparing its effects with those of the "pure" vasodilator nitroprusside.

Isovolumic relaxation: The absolute value of peak negative dP/dt decreased with both nitroprusside and nicardipine, reflecting at least in part the sensitivity of

this index to afterload.¹¹ The time constant of relaxation was shortened with nitroprusside, as has been demonstrated in studies of normal dogs,¹¹ as well as dogs¹⁵ and patients³ with systolic dysfunction, but not normal subjects.¹⁶ The decrease in the time constant may be attributable to altered loading conditions, reduced end-systolic volume, more synchronous LV relaxation with nitroprusside, or a combination of these.^{13,17}

The effects of calcium channel blockers on indexes of relaxation are dependent on the population studied and the route of administration. Calcium antagonists shorten relaxation in some^{18,19} but not in all²⁰ patients with hypertrophic cardiomyopathy. Verapamil does not

FIGURE 2. Left ventricular diastolic pressure-volume relations during the second baseline period (open triangles) and during administration of nicardipine (closed triangles) in 11 patients. A downward shift of the diastolic pressure-volume relation in the passive filling phase was present in 6 patients (A) and absent in 5 patients (B). Patient numbers are indicated in the lower right-hand corner of graphs.



alter T_D in patients with hypertension,²¹ and lengthens T_D in patients with aortic stenosis.¹⁹ Whereas the systemic administration of nifedipine or nicardipine to patients with coronary artery disease shortens relaxation,^{6,22} intracoronary nicardipine does not alter⁶ and intracoronary nifedipine slows^{22,23} relaxation. The mechanisms underlying these findings were clarified by Walsh and O'Rourke²⁴ in a study of conscious dogs. They found that intravenous administration of calcium antagonists did not change or shortened relaxation in the presence of intact reflexes, but did not change or prolonged relaxation in the presence of β blockade. Thus, any beneficial effect of calcium antagonists on isovolumic relaxation appeared to result from reflex sympathetic stimulation.

In the present study, the systemic administration of nicardipine to patients with systolic dysfunction resulting from coronary artery disease did not affect the speed of isovolumic relaxation. This result probably represents a balance between negative and positive influences on the speed of relaxation. The direct effect of calcium antagonists on myocardial relaxation appears to be negative, possibly because a reduction in cytosolic calcium concentration slows the rate of transfer of calcium from the contractile proteins to the sarcoplasmic reticulum.^{25,26} Possible counterbalancing positive influences on the speed of relaxation include reflex sympa-

thetic stimulation, decrease in end-systolic volume due to afterload reduction, and coronary vasodilation resulting in amelioration of ischemia and greater uniformity of relaxation. Blunting or absence of reflex sympathetic stimulation in response to vasodilation in patients with severe heart failure has been demonstrated previously.²⁷ In the present study, catecholamine levels were not measured, but heart rate did not change in response to either nitroprusside or nicardipine. End-systolic volume decreased with nicardipine, despite the drug's negative inotropic effect, as a result of afterload reduction. Finally, nicardipine may have ameliorated ischemia in our patients, although it would not be expected to improve nonuniformity of relaxation associated with scar from previous infarction.

Diastolic pressure-volume relation: Systemic vasodilator therapy with nitroprusside has been demonstrated to cause a downward shift in the LV diastolic pressure-volume relation in some patients with LV enlargement.^{3,9} The downward shift occurs with interventions that decrease preload, but not with those that reduce afterload only,¹⁰ and may be related to ventricular interaction within the constraints of the pericardium.²⁸ Nifedipine causes a downward shift in LV diastolic pressure-volume relation in some¹⁸ but not all²⁰ patients with hypertrophic cardiomyopathy. Verapamil does not shift the relation downward in most patients with hypertension²¹ or coronary artery disease with normal systolic function.⁵ In patients with dilated ventricles and high end-diastolic pressures, Ludbrook et al²⁹ demonstrated that nifedipine shifted the diastolic pressure-volume relation downward, and attributed the improvement in distensibility to lessening of external constraint to filling by the right ventricle.

In this study of patients with LV systolic dysfunction, the diastolic pressure-volume relation was shifted downward with nicardipine therapy in approximately half of the patients. Downward shifts did not result from diminished right ventricular distension, at least as judged from right atrial pressures. Thus, it is possible that nicardipine had a direct beneficial effect on LV distensibility. Evidence against such a specific effect of nicardipine comes from the presence of similar shifts with nitroprusside. Furthermore, the relation between end-diastolic pressure and volume was not shifted significantly with nicardipine.

Study limitations: The prolonged duration of action of nicardipine precluded administration of nitroprusside and nicardipine in randomized order. The results of an acute study of the effects of a drug on resting hemodynamic parameters may not be directly extrapolated to conclusions regarding chronic therapy.

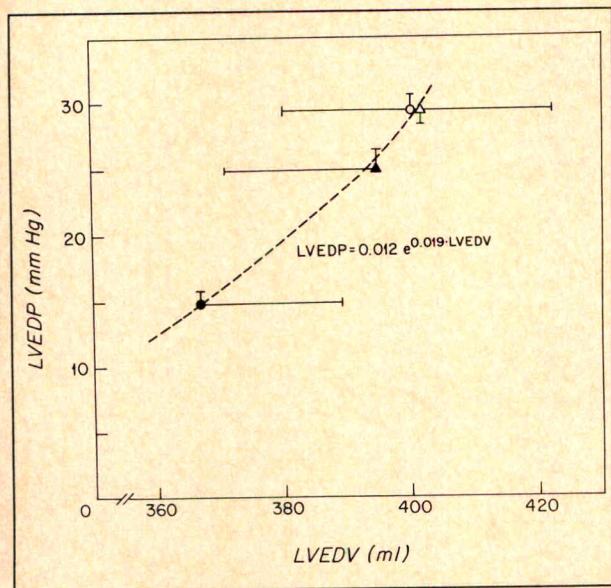


FIGURE 3. Pooled left ventricular end-diastolic pressure (LVEDP)-volume points for the first baseline (open circle), nitroprusside (closed circle), second baseline (open triangle) and nicardipine (closed triangle) periods. Error bars represent standard error of the mean. An exponential curve relating LVEDP to LV end-diastolic volume (LVEDV) was fit to the baseline and nitroprusside points. Nicardipine did not significantly shift the relation between end-diastolic pressure and volume away from the curve.

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A New Method for Estimating Preexcitation Index Without Extrastimulus Technique and Its Usefulness in Determining the Mechanism of Supraventricular Tachycardia

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The preexcitation index has been shown to be useful in determining the mechanism of paroxysmal supraventricular tachycardia (SVT) and the site of the accessory pathway in atrioventricular (AV) reentrant tachycardia. To test whether a preexcitation index could be computed analytically instead of by scanning the whole SVT cycle with extrastimuli, 19 patients with SVT were studied. The new index was computed using the following formula: (AV conduction time during SVT) + (ventriculoatrial conduction time during ventricular pacing at the SVT cycle length) – (SVT cycle length). There was a strong correlation between the preexcitation index determined by the extrastimulus technique and the new index in 15 patients in whom the preexcitation index could be determined ($r = 0.99$, $p < 0.01$). The value on the new index was >90 ms only in patients with dual AV nodal pathways. In the 4 patients in whom the preexcitation index could not be determined by the extrastimulus technique, the new index could differentiate AV reentrant tachycardia (index for 2 patients, 60 and 60 ms, respectively) from AV nodal reentrant tachycardia (index for 2 patients, 100 and 105 ms, respectively). In conclusion, the new index provided help in determining the mechanism of SVT, even when retrograde atrial preexcitation by a ventricular extrastimulus did not occur.

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A premature ventricular stimulus introduced at an appropriate moment during paroxysmal supraventricular tachycardia (SVT) may preexcite the subsequent atrial cycle. Retrograde atrial preexcitation has been used to verify the participation of an accessory pathway in the SVT circuit.^{1–3} Recently, a preexcitation index was proposed as an aid in distinguishing atrioventricular (AV) reentrant tachycardia from AV nodal reentrant tachycardia and determining the site of the accessory pathway in AV reentrant tachycardia.⁴

To determine the preexcitation index, the whole SVT cycle needs to be scanned by ventricular extrastimuli. This procedure is time-consuming and, in certain cases, inappropriate, particularly in patients with left-sided free wall accessory pathways or dual AV nodal pathways.^{2,4,5} The preexcitation index is affected mainly by the SVT cycle length, the distance between the pacing site and the reentrant circuit, and the refractory period of the pacing site.^{4–6} We hypothesized from this that the preexcitation index could be calculated analytically, using the ventriculoatrial conduction time during ventricular pacing and the AV conduction time during the SVT. The purpose of this study was to test this hypothesis.

METHODS

Study patients: The study group comprised 19 patients, 14 men and 5 women aged 12 to 68 years (mean \pm standard deviation 42 ± 15) with SVT who underwent electrophysiologic study in the drug-free state. Fourteen of 19 patients had orthodromic AV reentrant tachycardia⁷ (8 with manifest and 6 with concealed Wolff-Parkinson-White syndrome). The remaining 5 patients had AV nodal reentrant tachycardia.⁷ Patients were divided into 2 groups according to whether the preexcitation index could be determined by the extrastimulus technique (group A, 15 patients) or not (group B, 4 patients).

Electrophysiologic study: Multipolar electrode catheters (United States Catheters and Instruments, 6Fr) were introduced percutaneously and positioned in the high right atrium, right ventricular apex, His bundle region and, if possible, the coronary sinus. If an electrode catheter could not be introduced into the coronary sinus, a left atrial electrogram was recorded through an esophageal lead.⁸ The distal pair of electrodes were used for electrical stimulation, and the proximal pair for recording. Stimulation was performed with 2-ms rectangular pulses at twice the late diastolic threshold using a digital programmable stimulator (Fukuda Denshi, BC02). Intracardiac electrograms filtered at 30 to 500 Hz and electrocardiographic leads I, aVF, and V₁ were recorded simultaneously at paper speeds of 50 to 100 mm/s on an ink-jet recorder (Nihon Kohden, RIJ2108) and on an FM tape using a cassette tape recorder (TEAC MR-40) for later analysis.

Pacing protocol: In each patient, SVT with narrow QRS was induced by ventricular extrastimulation. A single extrastimulus was introduced during the SVT from the right ventricular apex. The coupling interval was shortened in 5-ms steps until either the ventricular effective refractory period was reached or the SVT was terminated. Atrial preexcitation by a ventricular extrastimulus during SVT was considered present (group A, 15 patients) when the atrial cycle length encompassing the ventricular premature complex decreased suddenly by ≥ 10 ms.⁴ In the remaining 4 patients (group B),

retrograde atrial preexcitation did not occur with a single ventricular extrastimulus. The preexcitation index was defined as the difference between the SVT cycle length and the longest coupling interval of the ventricular extrastimulus that preexcited the atria.⁴ During SVT, the anterograde conduction time (T1) from the earliest atrial activation among the recording sites to the right ventricular apex was determined. The retrograde conduction time (T2) from the right ventricular apex to the earliest atrial activation was determined during right ventricular pacing at SVT cycle length.

Analytical prediction of preexcitation index: Our new index was computed by the following formula: $T1 + T2 - CL$, where CL is the SVT cycle length (Figure 1). Figure 1 shows the fundamentals for constructing the formula. The right ventricular electrogram is recorded at EG1, and the earliest atrial activation at EG2. The exit and entry of the reentrant circuit are supposed to be located at the same site, i.e., point P. T1 is the anterograde conduction time from EG2 to EG1 during SVT, which is equal to the SVT cycle length minus Z plus Y (Figure 1A). T2 is the retrograde conduction time from EG1 to EG2 during ventricular pacing at the SVT cycle length, which is equal to X plus Z (Figure 1B). For the wave front produced by an extrastimulus from EG1 to collide with the spontaneous orthodromic wave front at point P, the spontaneous wave front should be located at point Q, which lies by time X short of point P (Figure 1C). It is time X plus Y before

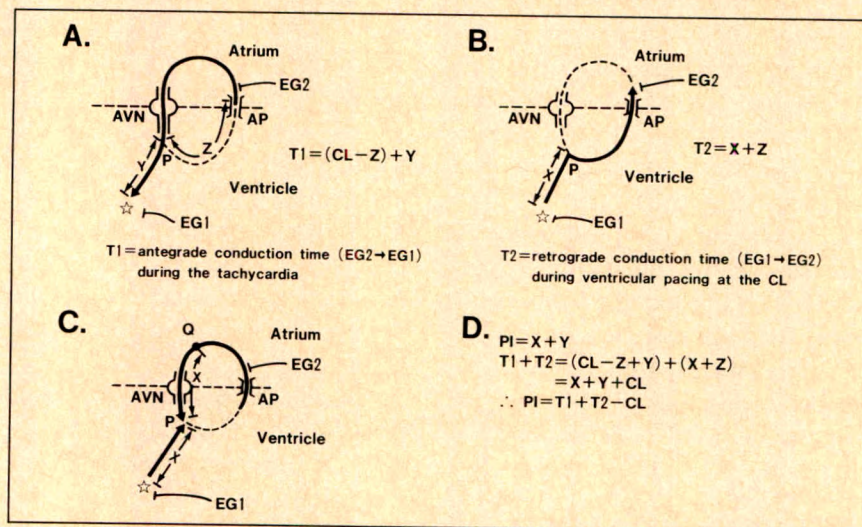


FIGURE 1. Schema for estimating the preexcitation index (PI) in patients with atrioventricular reentrant tachycardia. In this figure, the entry site is the same as the exit site (point P). The right ventricular electrogram is recorded at EG1, and the earliest atrial activation site at EG2. **A**, T1 is the anterograde conduction time from EG2 to EG1 during atrioventricular reentrant tachycardia, which is equal to the tachycardia cycle length (CL) minus Z (conduction time from point P to EG2) plus Y (conduction time from point P to EG1). **B**, T2 is the retrograde conduction time from EG1 to EG2 during ventricular pacing at CL, which is equal to X (conduction time from EG1 to point P) plus Z. **C**, for the wave front produced by an extrastimulus delivered from EG1 to collide with the spontaneous orthodromic wave front at point P, the extrastimulus should be delivered when the spontaneous orthodromic wave front is located at point Q, which lies by time X short of point P. This indicates that the preexcitation index equals time X plus Y. Time X and Y can be computed mathematically, as shown in **D**. See text for details. AP = accessory pathway; AVN = atrioventricular node. Star indicates the pacing site.

TABLE I Electrophysiologic Data

Pt. No.	Age (yr) & Sex	Type of PSVT	PI (ms)	T1 (ms)	T2 (ms)	CL (ms)	Our Index (ms)
Group A							
1	25F	cWPW	40	200	130	300	30
2	27M	WPW	70	160	160	270	50
3	30M	cWPW	60	160	220	320	60
4	36M	cWPW	60	290	160	400	50
5	39M	WPW	40	200	140	310	30
6	47M	cWPW	50	250	130	340	40
7	49M	WPW	60	170	180	300	50
8	49M	WPW	10	190	130	310	10
9	52F	WPW	80	220	150	310	60
10	53M	cWPW	110	230	210	350	90
11	62M	cWPW	70	300	180	420	60
12	68M	WPW	60	200	150	300	50
13	39M	AVNRT	110	240	180	320	100
14	53M	AVNRT	100	230	160	300	90
15	60F	AVNRT	190	440	180	450	170
Group B							
1	12M	WPW	—	220	110	270	60
2	19M	WPW	—	190	130	260	60
3	29F	AVNRT	—	370	120	390	100
4	45F	AVNRT	—	260	110	265	105

AVNRT = atrioventricular nodal reentrant tachycardia; c = concealed; CL = cycle length of paroxysmal supraventricular tachycardia; PI = preexcitation index; PSVT = paroxysmal supraventricular tachycardia; T1 = atrioventricular conduction time during paroxysmal supraventricular tachycardia; T2 = ventriculoatrial conduction time during right ventricular pacing at the cycle length; WPW = Wolff-Parkinson-White syndrome.
Our index is computed as $T1 + T2 - \text{cycle length}$.

the orthodromic wave front is expected to reach EG1, when the orthodromic wave front lies at point Q. This indicates that the preexcitation index equals time X plus Y. Time X plus Y cannot be determined by conventional electrophysiologic study, but can be calculated mathematically, as shown in Figure 1D. Our index calculated by this formula was compared with the preexcitation index determined by the extrastimulus technique in group A patients. Additionally, we tested whether our index could differentiate AV reentrant tachycardia from AV nodal reentrant tachycardia in group B patients, in whom retrograde atrial preexcitation did not occur with the extrastimulus technique.

Statistical analysis: Data are expressed as means \pm standard deviation. The relation between the preexcitation index and our index was evaluated by linear regression analysis. Statistical significance was set at $p < 0.05$.

RESULTS

Relation between preexcitation index and our index: Pertinent data are summarized in Table I. A representative example is illustrated in Figure 2. In a patient (no. 4) with a left-sided accessory pathway and an SVT cycle length of 400 ms, atrial preexcitation first occurred with a ventricular extrastimulus at a coupling interval of 340 ms (Figure 2A). Consequently, the preexcitation index was 60 ms (400 minus 340 ms).

During the SVT, the earliest atrial activation was located in the region of the coronary sinus, and the antero-grade conduction time (T1) from the coronary sinus region to the right ventricular apex was 290 ms (Figure 2A). Ventricular pacing during sinus rhythm at the SVT cycle length revealed that retrograde conduction time (T2) from the right ventricular apex to the coronary sinus region was 160 ms (Figure 2B). Therefore, our index was calculated as 50 ms ($T1 + T2 - CL = 290 + 160 - 400$ ms) according to the formula (Figure 1). Linear regression analysis revealed a strong correlation between the preexcitation index and our index in group A patients ($r = 0.99$, $p < 0.01$, Figure 3). Our index was about 10 ms shorter than the preexcitation index determined by the extrastimulus technique. In 3 patients with AV nodal reentrant tachycardia, the preexcitation index was longer than 100 ms, a finding consistent with the previous study.⁴ Our index was >90 ms only in patients with AV nodal reentrant tachycardia.

Usefulness of our index in determining the mechanism of supraventricular tachycardia: In group B patients (2 with a left-sided free wall accessory pathway, 2 with dual AV nodal pathways), retrograde atrial preexcitation by a ventricular extrastimulus during SVT did not occur. Our indexes were 60 ms in 2 patients with a left-sided free wall accessory pathway, and 100 ms and 105 ms, respectively, in 2 patients with dual AV nodal pathways. When a value of 90 ms on our index was selected as a cut-off point, the sensitivity and specificity for diagnosing AV nodal reentrant tachycardia were 80 and 100%, respectively, in our 19 patients.

DISCUSSION

The major findings of this study are that our new index was almost identical with the preexcitation index determined by the extrastimulus technique, and that our index was useful in determining the mechanism of SVT even when ventricular extrastimuli failed to preexcite the atria.

Preexcitation index: SVTs are frequently due to 2 mechanisms: AV nodal reentry and orthodromic AV reentry by an accessory pathway. Several electrophysiologic criteria have been reported to distinguish these 2 mechanisms.^{1-5,9-11} However, these criteria have limitations. Miles et al⁴ proposed the concept of "preexcitation index" as a more useful way to determine the mechanism of SVT and to predict the site of the accessory pathway in AV reentrant tachycardia. A preexcitation index >75 ms occurred only with a left-sided free wall accessory pathway or dual AV nodal pathways, and a preexcitation index <45 ms only with a septal accessory pathway.⁴

In patients with a left-sided free wall accessory pathway or dual AV nodal pathways, retrograde atrial preexcitation sometimes cannot be demonstrated by introducing a single extrastimulus scanning the whole SVT cycle.^{2,4,5,9} The preexcitation index is limited in its

use by the refractory period of the pacing site,^{6,9} and cannot differentiate AV reentrant tachycardia with a left-sided free wall accessory pathway from AV nodal reentrant tachycardia.⁴ A previous report demonstrated the role of the stimulating site in the occurrence of atrial preexcitation.⁵ Other investigators showed the advantage of introducing double ventricular extrastimuli to demonstrate atrial preexcitation in patients with a left-sided free wall accessory pathway.⁶ Changing the stimulating site or increasing the number of extrastimuli is an alternative way to manifest atrial preexcitation.^{5,6} However, this makes the procedure much more time-consuming, and the preexcitation index measured by these methods becomes too complicated for clinical usage.

Methodologic considerations: This study presented an easier and faster way to determine an index almost identical to the preexcitation index. Our index was as effective as the preexcitation index⁴ in determining the SVT mechanism. In addition, our index could be applied to patients in whom retrograde atrial preexcitation could not be demonstrated with ventricular extrastimuli, because it is not affected by the refractory period of the pacing site.

Our index was almost 10 ms shorter than the preexcitation index determined by the extrastimulus technique (Figure 3). If the preexcitation index were defined using the coupling interval at which the antidromic wave front produced by an extrastimulus collided with the spontaneous wave front at the exit of the reen-

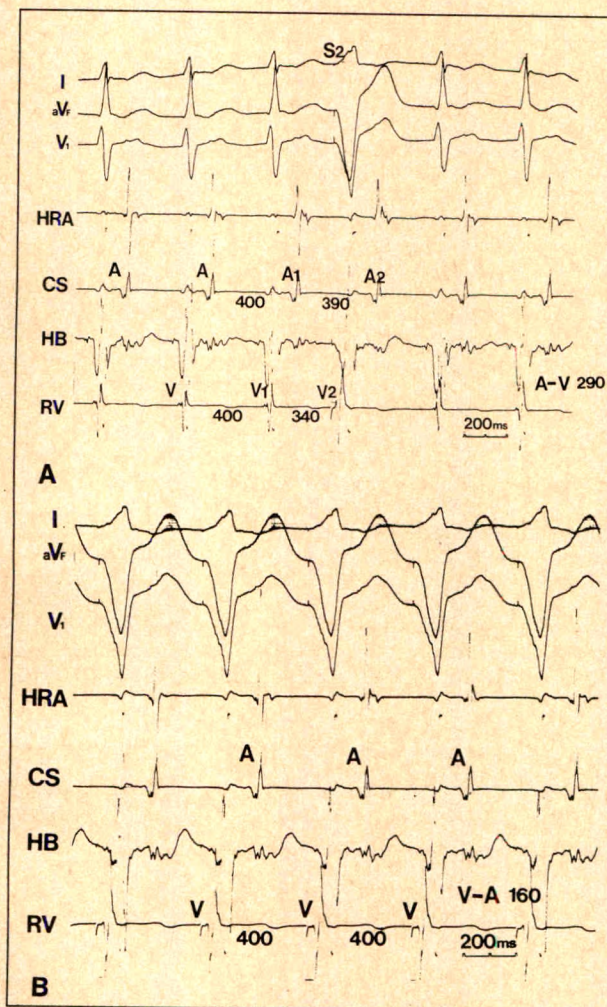


FIGURE 2. Representative example of calculating our index in a patient with a left-sided accessory pathway (patient no. 4). Electrocardiographic leads I, aVF, and V₁, and electrograms recorded at the high right atrium (HRA), coronary sinus (CS), His bundle region (HB) and right ventricle (RV) are arranged from top to bottom. A, during reciprocating tachycardia with a cycle length of 400 ms, the earliest atrial activation site was located in the coronary sinus region. The anterograde conduction time (T₁) from the earliest atrial activation site to the right ventricle was 290 ms. Retrograde atrial preexcitation in response to an extrastimulus (S₂) from the right ventricular apex occurred. Atrial preexcitation did not occur in this patient until the coupling interval of the ventricular extrastimulus was decreased to 340 ms, at which time the A₁ to A₂ interval decreased from 400 to 390 ms. The preexcitation index was therefore 60 ms (400 - 340 ms). B, right ventricular pacing during sinus rhythm at a cycle length of 400 ms revealed that the retrograde conduction time (T₂) from the right ventricle to the coronary sinus region was 160 ms. Consequently, our index was 50 ms (290 + 160 - 400 ms), close to the preexcitation index. A₁, V₁ = spontaneous atrial and ventricular complex during the tachycardia; A₂, V₂ = atrial and ventricular complex produced by S₂; A-V = atrioventricular conduction time, i.e., T₁; V-A = ventriculoatrial conduction time, i.e., T₂.

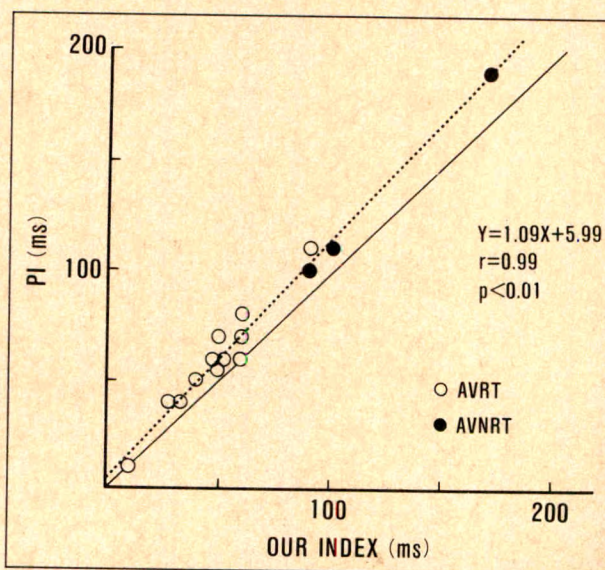


FIGURE 3. Relation between the preexcitation index (PI), ordinate, and our index, abscissa. Open circles indicate patients with atrioventricular reentrant tachycardia (AVRT), and closed circles patients with atrioventricular nodal reentrant tachycardia (AVNRT). There was a strong correlation between the 2 indexes. The solid line and dashed line represent a line of identity and a regression line ($Y = 1.09X + 5.99$), respectively.

trant circuit and not with the coupling interval at which retrograde atrial preexcitation ≥ 10 ms occurred, the preexcitation index would be almost the same as our index.

Although we considered our index to be almost identical to the preexcitation index,⁴ it could be differentiated from the preexcitation index. At shorter coupling intervals of extrastimuli, the preexcited atrial interval would be slightly longer than the ventricular interval because of the rate-dependent depression of intraventricular conduction.¹² Prematurity of ventricular extrastimuli would be increased to manifest retrograde atrial preexcitation. Consequently, the preexcitation index cannot correctly reflect the distance between the pacing site and the reentrant circuit in cases with a high preexcitation index. In contrast to the preexcitation index, our index could differentiate AV reentrant tachycardia with a left-sided free wall accessory pathway from AV nodal reentrant tachycardia. This might be because our index is not dependent on the rate-dependent conduction delay. The components (T1, T2, CL) used to calculate our index are the conduction time determined at the same basic cycle length, i.e., the SVT cycle length.

Clinical implications: The advantages of our index over the preexcitation index are as follows. First, our method saves time, because the whole SVT cycle does not need to be scanned. Second, our method can be applied to patients in whom SVT is not sustained. Third, our index is not affected by the refractory period of the pacing site or rate-dependent conduction delay. Therefore, our method can be used in patients in whom ventricular extrastimuli failed to preexcite the atria. From the present study, however, we should not con-

clude that the whole SVT cycle does not need to be scanned by ventricular extrastimuli. Induction of ventricular extrastimuli during SVT is still mandatory to exclude the presence of additional accessory pathways or intraatrial reentry.

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Usefulness of the Electrophysiology Laboratory for Evaluation of Proarrhythmic Drug Response in Coronary Artery Disease

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Two potential manifestations of proarrhythmic responses to type IA antiarrhythmic agents in the electrophysiology laboratory were evaluated in 122 patients with chronic coronary artery disease and previous myocardial infarction: (1) conversion of uniform nonsustained ventricular tachycardia (VT) into sustained VT after drug administration, and (2) induction of sustained VT by fewer extrastimuli after drug administration. Forty-two patients were evaluated for nonsustained VT. Eighty patients were evaluated for sustained VT: 30 of these had spontaneous sustained VT only while receiving empiric therapy with quinidine or procainamide, whereas the remaining 50 developed spontaneous VT in the absence of antiarrhythmic drugs. All patients underwent programmed stimulation in the baseline state and after procainamide. Four patients had conversion of induced uniform nonsustained VT into the same morphology, but sustained VT after procainamide administration. These responses only occurred in patients evaluated for nonsustained VT.

Over 90% of patients presenting with sustained VT had uniform sustained VT induced at the baseline study and after procainamide, regardless of whether the spontaneous arrhythmia occurred only in the presence or absence of antiarrhythmic drugs. There was no significant difference in the change in mode of induction from baseline to procainamide study, regardless of whether patients had developed spontaneous VT

only in the presence or absence of antiarrhythmic drugs. One patient with no inducible VT at the baseline study had inducible uniform sustained VT after procainamide administration, and 1 patient with inducible VT at baseline developed spontaneous sustained uniform VT after procainamide administration. Both patients had developed spontaneous sustained VT only while receiving therapy with type IA agents.

It is concluded that potential proarrhythmic effects may be observed in response to procainamide administration in the electrophysiology laboratory, but that this response is unusual in this population of patients with chronic coronary artery disease and ventricular arrhythmias: in 4 of 42 patients (10%) with spontaneous nonsustained VT, and 2 of 80 patients (2.5%) presenting with spontaneous sustained VT. It is premature to consider a decrease in the number of extrastimuli required to induce sustained VT after drug administration as a proarrhythmic drug effect.

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Electrophysiologists are frequently asked to evaluate patients who have developed arrhythmias only during empiric treatment with antiarrhythmic agents for asymptomatic arrhythmias such as ventricular premature complexes or nonsustained ventricular tachycardia (VT). It is often unclear in such cases whether the spontaneous arrhythmia was facilitated by the antiarrhythmic agent (a manifestation of a "proarrhythmic" effect), or whether the event represented failure of the drug to prevent an arrhythmia that would have occurred even in the absence of the antiarrhythmic agent.

Previous reports have used many definitions of proarrhythmic drug effects, and investigators have used varied techniques to assess the proarrhythmic effects of drugs.¹⁻¹¹ Studies using programmed stimulation have demonstrated that administration of antiarrhyth-

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TABLE I Patient Data

Group	Gender (% Male)	Age (yrs)	LVEF (%)	No Spontaneous Episodes of VT-S
1	86	61 ± 10.0	39 ± 14.3*	—
2	90	61 ± 9.7	27 ± 10.0	2.8 ± 2.4
3	88	58 ± 11.2	31 ± 13.7	2.6 ± 2.6

* $p < 0.05$ vs groups 2 and 3.
Results are expressed as mean ± standard deviation.
LVEF = left ventricular ejection fraction; VT-S = sustained VT.

mic drugs may change the arrhythmia induced from self-terminating to a sustained event. The responses reported, however, have varied, including changing inducible polymorphic nonsustained VT to uniform sustained VT¹⁰ and conversion of nonsustained uniform VT to a similar but different sustained VT morphology⁷ or sustained polymorphic VT.^{4,9} Other reports have noted no VT induction during the baseline study, followed by induction of sustained VT after drug.^{8,11}

Other phenomena in the electrophysiology laboratory have been proposed as representing proarrhythmia. One frequently cited proposed manifestation of proarrhythmic response is a change in the mode of induction from a "more" to "less" aggressive stimulation protocol (induction of VT by fewer extrastimuli after drug).⁴⁻⁹ However, none of these studies have attempted to correlate these observations with clinical events.

In this report, we analyze 2 potential electrophysiologic manifestations of so-called proarrhythmia in patients with chronic coronary artery disease and ventricular arrhythmias: (1) conversion of induced uniform nonsustained VT into sustained VT after drug administration, and (2) alteration in the inducibility of VT and in the mode of induction of VT by procainamide.

METHODS

Patient population: We studied 3 groups of patients with coronary artery disease and remote myocardial infarction. The first comprised 42 consecutive patients referred for electrophysiologic evaluation of nonsustained VT (group 1). In each case spontaneous nonsustained VT was documented in the absence of antiarrhythmic medication. Nineteen of these 42 had a history of syncope: 5 patients developed syncope only after receiving type IA antiarrhythmic agents (procainamide: 3 patients; quinidine: 2 patients) as empiric therapy for asymptomatic nonsustained VT, whereas the other 14 developed syncope in the absence of antiarrhythmic agents. The remaining 23 patients had no history of syncope.

The second and third groups comprised 80 consecutive patients, all of whom had coronary artery disease

and previous myocardial infarction, who were referred for evaluation of electrocardiographically documented, hemodynamically stable, uniform sustained VT. Thirty of these (group 2) developed spontaneous sustained VT only after receiving type IA antiarrhythmic agents empirically (quinidine: 8 patients; procainamide: 22 patients). The remaining 50 patients (group 3) presented with sustained VT in the absence of antiarrhythmic drugs. We chose to evaluate group 2 because in each case the arrhythmia occurred *only* in the presence of procainamide or quinidine. Thus, in group 2 patients, the arrhythmia might have resulted from a proarrhythmic drug effect. Group 3 was chosen as a control group in whom antiarrhythmic drugs could not have contributed to the development of spontaneous VT. Patient gender and age were similar for all 3 groups but the left ventricular ejection fraction was significantly higher for group 1 than groups 2 and 3 (Table I).

No patient had evidence of the drug-induced or idiopathic long QT syndrome. No patient had evidence of acute myocardial infarction at the time of or subsequent to the spontaneous arrhythmic event, and no patient had unstable angina.

Procedure: All patients underwent programmed stimulation after all antiarrhythmic agents were discontinued for ≥ 5 half-lives. Written informed consent was obtained in all cases. Programmed stimulation was performed using a custom-designed digital stimulator (Bloom Associates, Reading, Pennsylvania) that delivered rectangular pulses 1 ms in duration. An 8-beat drive followed by 1 to 3 extrastimuli was delivered. A 2- or 3-second pause was inserted between each test. At least 2 drive cycle lengths were used in each patient (usually 600 and 400 ms). Bursts of 5 to 15 beats, separated by 2 to 3 seconds at cycle lengths of 350 to 250 ms, were delivered in each case before delivery of triple extrastimuli. In patients with nonsustained VT or syncope, ≥ 2 right ventricular sites were stimulated. In patients presenting with sustained uniform VT, if programmed stimulation at 2 right ventricular sites failed to induce sustained VT, left ventricular stimulation was performed using the same protocol. Up to 3 extrastimu-

li at each cycle length and site were delivered in addition to burst pacing at cycle lengths of 350 to 250 ms. The sequence for programmed stimulation was as follows: a single extrastimulus was delivered in late diastole with the coupling interval reduced by 10 ms until ventricular refractoriness was reached or sustained VT was induced. If a single extrastimulus failed to induce sustained VT or ventricular fibrillation, a second extrastimulus was added: the first extrastimulus was placed ≥ 40 ms above refractoriness, and the interval from the first to second extrastimulus was equal to the interval from the last complex of the drive to the first extrastimulus. The second extrastimulus was decreased in 10-ms decrements until refractoriness was reached, at which time the first extrastimulus was moved 10 ms earlier. This sequence was repeated until sustained VT was induced or both extrastimuli reached refractoriness. If no sustained VT was induced, a third extrastimulus was added; the first extrastimulus was again placed ≥ 40 ms above the effective refractory period and each subsequent extrastimulus was initially placed at the same interval above the previous extrastimulus. The interval from the second to third extrastimulus was decreased by 10-ms decrements until it failed to capture, at which time the coupling interval from the first to second extrastimulus was decreased by 10 ms in the manner described earlier. All steps in the stimulation protocol were performed first at the right ventricular apex, then at the outflow tract—that is, single extrastimuli were delivered at the apex, then at the outflow tract, followed by double extrastimuli at the apex and outflow tract, etc. The end point of the stimulation protocol was induction of sustained VT or completion of the protocol to refractoriness of all 3 extrastimuli.

Surface electrocardiographic leads (I, II or aVF, V₁) were recorded on a multichannel oscilloscope (Electronics for Medicine VR16) together with bipolar intracardiac electrograms from the right ventricular stimulating catheters (filtered at 30 to 500 Hz). If sustained VT was induced, a 12-lead electrocardiogram was recorded. Data were recorded simultaneously using an ink-jet recorder (Siemens Mingograph) and magnetic tape (Honeywell model 5600C).

After completion of the baseline stimulation protocol, all patients received procainamide. Procainamide was infused at a rate of 50 mg/min to a total dose of 15 mg/kg. The infusion rate was then decreased to 0.11 mg/kg/min. After 5 minutes at this infusion rate, a serum specimen for procainamide level was obtained and stimulation was commenced. This protocol for procainamide administration was used because we have found it useful in maintaining a relatively constant level

for the duration (20 to 30 minutes) of programmed stimulation during the test.¹² Programmed stimulation was performed after procainamide in the same fashion as described earlier during the baseline state.

Definitions: Sustained VT was defined as tachycardia lasting >30 seconds or requiring termination in <30 seconds because of hemodynamic decompensation in the laboratory.

Nonsustained VT was defined as VT lasting from 3 beats to 30 seconds, terminating spontaneously, at rates of ≥ 120 beats/min.

Uniform VT was defined as a single morphology, constant in ≥ 3 recorded electrocardiographic leads for the majority of an episode of tachycardia.

The ventricular effective refractory period was defined as the longest S₁ to S₂ interval that failed to capture the ventricle. For this study this value was determined at a paced cycle length of 600 ms, unless the sinus rate made it necessary to pace at a shorter cycle length.

Statistical analysis: Data are presented as mean \pm standard deviation. Statistical comparison of continuous variables was performed using the unpaired *t* test. Analysis of variance was used to compare values among the 3 patient groups. A *p* value ≤ 0.05 was considered statistically significant.

RESULTS

Group 1: Programmed stimulation in the baseline state induced only nonsustained uniform VT in 9 of the 42 patients, both nonsustained and sustained uniform VT in 6 patients, only sustained uniform VT in 17 patients, and only polymorphic VT in 6 patients. Four patients had no inducible VT. Of the patients in whom only uniform nonsustained VT was induced, morphology varied in 2 (staying constant in 1 morphology for 3 or 4 complexes and then switching to a second morphology for 2 to 5 complexes), whereas in the remaining 4 patients only a single morphology was induced (Table II). In 5 patients, the nonsustained uniform tachycardia induction was reproducible (the induction was repeated ≥ 5 times), whereas in 1 the tachycardia could be induced only once, despite multiple attempts. The nonsustained uniform tachycardias were induced by a single extrastimulus in 4 patients, by double extrastimuli in 3 patients and by triple extrastimuli in 8 patients. In each patient the stimulation protocol was completed through triple extrastimuli to refractoriness of each extrastimulus without induction of any sustained tachycardia in the baseline state.

Programmed stimulation after procainamide administration failed to induce any VT in 11 of the 42 pa-

TABLE II Results of Electrophysiologic Studies in Patients Presenting with Nonsustained Ventricular Tachycardia (Group I)

Patients	Baseline VRP (ms)	Procainamide VRP (ms)	Increase in VRP (%)	Baseline VTCL (ms)	Procainamide VTCL (ms)	Increase in VTCL (%)	Procainamide Level (mg/liter)	Baseline: No. of Cycles of Uniform VT Induced
Patients Converting from Uniform Nonsustained to Sustained VT After Procainamide								
1	260.00	270.00	4	240.00	310.00	29	11.70	2
2	270.00	310.00	15	220.00	280.00	27	12.70	10
3	260.00	290.00	12	230.00	330.00	43	11.00	18
4	300.00	300.00	0	230.00	260.00	13	5.00	6
n = 4 Mean	272.50	292.50	8	230.00	295.00	28	10.10	
SD	18.93	17.08		8.16	31.09		3.47	
Patients with No VT Inducible After Procainamide								
n = 11 Mean	241.00	257.00	7	270.00			10.18	
SD	22.34	27.51		78.26			2.35	
Patients with VT Inducible After Procainamide								
n = 27 Mean	250.83	277.50	11	244.09	308.64	26	10.20	
SD	30.88	29.27		26.35	48.38		3.74	

SD = standard deviation; VRP = measured ventricular effective refractory period; VT = ventricular tachycardia; VTCL = cycle length of induced ventricular tachycardias, with same morphology before and after procainamide.
Subgroups of group 1 did not differ significantly from each other in any parameter.

tients, whereas uniform nonsustained VT only was induced in 9 patients, and uniform sustained VT was induced after procainamide administration in 21 patients. Induction of polymorphic VT persisted in 1 patient. Three patients who had uniform sustained VT induced in the baseline state had the same morphology induced as only nonsustained VT after procainamide.

Four patients with nonsustained uniform VT induced in the baseline study (by double and triple extrastimuli in 1 patient and triple extrastimuli only in 3)

had sustained VT induced by 3 extrastimuli after procainamide. In each patient the induced sustained VT had the same morphology as the nonsustained uniform tachycardia (Figure 1). Examination of the right ventricular electrograms revealed that both the appearance and the timing of the local electrograms relative to the QRS complexes were the same during the induced nonsustained and sustained tachycardias (Figure 1). The mean cycle length of VT induced after procainamide in this group increased by 28%. The 4 patients whose re-

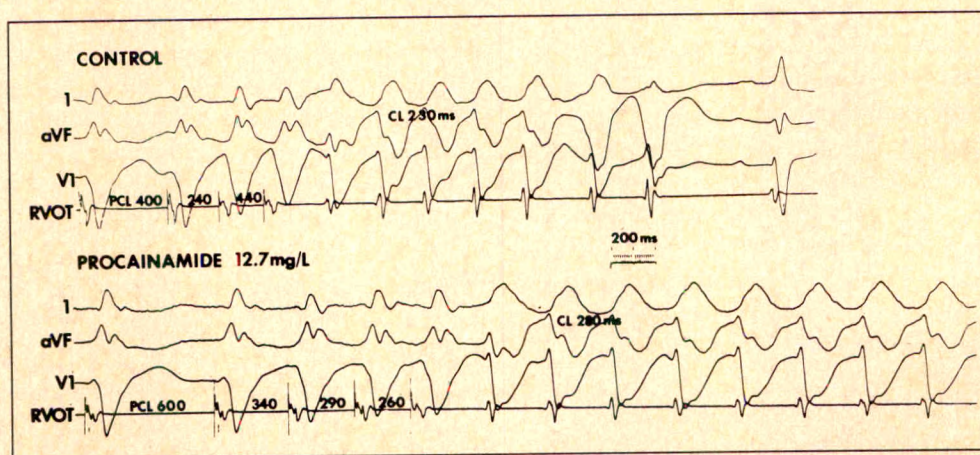


FIGURE 1. Programmed stimulation in the control state and after procainamide in 1 of 4 patients in whom procainamide converted nonsustained into sustained uniform tachycardia. *Top*, during control tracing, double ventricular extrastimuli delivered during a drive cycle length (CL) of 400 ms induce a 7-beat run of nonsustained ventricular tachycardia. The first 5 beats have a left bundle branch block morphology. The tachycardia then abruptly slows and terminates. The cycle length of the first 5 beats is 230 ms. After procainamide administration, resulting in a serum level of 12.7 mg/liter, triple extrastimuli delivered at the right ventricular outflow tract (RVOT) at a paced cycle length (PCL) of 600 ms induce sustained ventricular tachycardia, having the same morphology as the first 5 complexes of the nonsustained ventricular tachycardia. The cycle length of the tachycardia induced after procainamide is prolonged to 280 ms. This tachycardia required cardioversion to terminate. Note that the morphology and timing of the right ventricular outflow tract electrogram remains constant before and after procainamide. In each tracing, surface electrocardiographic leads I, aVF and V₁ are displayed, followed by local ventricular electrograms from the right ventricular outflow tract.

sponses to programmed stimulation changed from non-sustained to sustained VT with the same morphology had syncope only while receiving antiarrhythmic drugs. No other patient in the study demonstrated a conversion from inducible nonsustained VT to any inducible uniform sustained VT after procainamide.

The effects of procainamide on the measured ventricular refractory periods and cycle lengths of induced VTs did not differ significantly in the 4 patients converting from nonsustained to sustained VT versus the other group 1 patients (Table II). In 2 of the 3 patients in whom sustained uniform VT was induced at baseline study, and in whom the same morphology was only nonsustained after procainamide, the number of extrastimuli that induced the VT decreased from triple to double after procainamide (the same nonsustained VT was also induced by triple extrastimuli after procainamide). The mean procainamide level in the 2 patients was 10.3 ± 5.9 mg/liter. Their measured mean ventricular effective refractory period increased by 10%, from 237 ± 6 to 260 ms, and their mean VT cycle length increased by 53%, from 200 ± 30 to 302 ± 45 ms after procainamide.

Group 2: Sustained uniform VT was induced in the absence of drugs in 29 of 30 patients (97%) who had presented with spontaneous sustained VT only while receiving antiarrhythmic drugs. VT was induced by a single extrastimulus in 24% of 30 patients, in 45% by 2 extrastimuli, and 28% by 3 extrastimuli. Sustained VT was induced by right ventricular stimulation in all patients. One patient repeatedly developed sustained VT spontaneously during induced atrioventricular nodal reentry. After procainamide administration, sustained VT was induced in 29 patients. One patient, in whom no VT was inducible in the baseline state, had uniform sustained VT induced by rapid ventricular pacing after procainamide. Another patient, who had sustained VT induced by a single extrastimulus in the baseline state, had the same morphology of sustained VT induced by rapid pacing, which then occurred spontaneously after procainamide. The patient who developed VT during atrioventricular node reentry in the baseline state had VT induced by rapid pacing after procainamide. No patient in this group with uniform sustained VT induced in the baseline state had the same morphology of VT but only nonsustained VT induced after procainamide.

After procainamide administration, fewer extrastimuli were required for induction of sustained VT after procainamide administration in 43% of 30 patients (Figure 2).

Group 3: Sustained uniform VT was induced in the absence of drugs in 47 of 50 patients (94%) who had

presented with spontaneous sustained VT in the absence of antiarrhythmic drugs. The sustained VT was induced by a single extrastimulus in 11% of patients, by 2 extrastimuli in 52%, by rapid pacing in 4%, and by 3 extrastimuli in 33%. After procainamide in this group, inducible sustained VT persisted in 44 of the 47 patients, only nonsustained VT could be induced in 1 patient, and in 2 patients no VT could be induced. The patient for whom only nonsustained VT could be induced after procainamide had the same morphology of VT induced by triple ventricular extrastimuli both before and after drug administration. In this patient, the measured ventricular refractory period increased by 11% and the VT cycle length by 27% after procainamide. There was a decrease in the number of extrastimuli required to induce sustained VT after procainamide in 37% of patients (Figure 2). The modes of VT induction before and after procainamide, and the change in the mode of induction in individual patients, did not differ significantly between groups 2 and 3. Sustained VT was inducible by right ventricular stimulation in all patients. There was no significant difference in the effects of procainamide on measured ventricular refractoriness or induced VT cycle lengths among patients in groups 1, 2, and 3 (Tables II and III), nor did the procainamide levels achieved differ among these patients (Tables II and III).

DISCUSSION

This study demonstrates a number of limitations of programmed stimulation in evaluating patients for possible proarrhythmic effects of antiarrhythmic drugs. First, although most electrophysiologists would concede that reproducible conversion of a self-terminating, brief

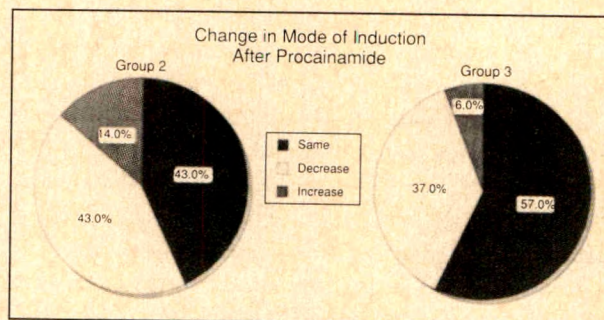


FIGURE 2. Comparison between the change in mode of induction of sustained ventricular tachycardia after administration of procainamide and the baseline electrophysiologic study. Same, decrease and increase refer to the number of extrastimuli required to induce sustained ventricular tachycardia in each patient. Group 2 comprises patients having spontaneous VT only in the presence of procainamide or quinidine. Group 3 comprises patients having spontaneous sustained VT in the absence of antiarrhythmic drugs. There is no significant difference in the distribution of change in modes of induction between groups 2 and 3.

TABLE III Results of Electrophysiologic Studies in Patients Presenting with Sustained Ventricular Tachycardia

Patients	Baseline VRP (ms)	Procainamide VRP (ms)	Increase in VRP (%)	Baseline VTCL (ms)	Procainamide VTCL (ms)	Increase in VTCL (%)	Procainamide Level (mg/liter)
Patients with Spontaneous Sustained VT Only with Antiarrhythmic Agents (Group 2)							
n = 30	Mean 248.16	270.53	9	299.12	394.12	34	9.91
	SD 33.22	33.74		58.82	57.23		2.62
Patients with Spontaneous Sustained VT in the Absence of Antiarrhythmic Agents (Group 3)							
n = 50	Mean 257.00	281.33	10	272.97	342.03	26	9.11
	SD 27.81	34.31		57.02	70.1		3.00
Group 2 did not differ significantly from group 3 in any parameter. Abbreviations as in Table II.							

arrhythmia into a sustained one should be considered a true proarrhythmic effect, this cannot be documented in the electrophysiology laboratory very frequently in patients with chronic coronary artery disease. We have observed this finding in only 10% of 42 patients undergoing evaluation for nonsustained VT, and in none of 80 patients undergoing evaluation for spontaneous sustained VT. Although some workers have classified as proarrhythmic the new induction of polymorphic VT or ventricular fibrillation after drug administration,^{4,9,10} the clinical significance of these induced arrhythmias is questionable.

It is possible that the difference in response to programmed stimulation before and after procainamide represents random variation. However, this seems unlikely, because in 3 of 4 patients, multiple episodes of the same nonsustained tachycardia were induced during the baseline study and, in the fourth patient, multiple attempts failed to induce sustained VT. Because induction of the sustained tachycardia after procainamide required 3 extrastimuli in each patient, it is also conceivable that if ≥ 4 extrastimuli had been delivered during the baseline protocol, sustained tachycardia would have been induced. However, the stimulation protocol using 3 extrastimuli was adequate to induce sustained VT in $>90\%$ of our patients who presented with spontaneous sustained VT. Although it is possible that these responses represent drug toxicity, the procainamide levels and degrees of change in refractoriness and induced tachycardia cycle length were similar to those observed in groups 2 and 3. These drug levels are modest, and in the range usually required to prevent induction of sustained VT.¹³

Another limitation of our observations is that we monitored only 3 surface electrocardiogram leads simultaneously. It is possible that the nonsustained and sustained tachycardias induced were not really the same. We cannot totally exclude this possibility. However, these 3 electrocardiographic leads represent ap-

proximately orthogonal recordings, thus giving a fairly complete picture of ventricular activation. In addition, intracardiac right ventricular electrographic morphology and timing also remained constant.

We are unaware of any previous report demonstrating conversion of a uniform nonsustained VT induced at baseline study into a sustained tachycardia having the same morphology after drug administration when a full stimulation protocol with 3 extrastimuli is used. This occurrence is important because it would support the idea that a drug could alter the electrophysiologic properties of a potential reentrant circuit, converting it from one that could not sustain itself in the absence of drug to a more stable self-sustaining circuit.

We observed 2 other potential manifestations of proarrhythmic drug effects. It seems reasonable to assume that the responses observed in the group 2 patient who had no VT inducible at the baseline study but who had uniform VT induced only after procainamide, and in the group 2 patient who developed spontaneous VT after procainamide, represent proarrhythmic drug effects. It is noteworthy that both patients were in the group who only developed spontaneous sustained VT while receiving empiric antiarrhythmic therapy (in both cases with procainamide).

A wide variety of antiarrhythmic drug effects have been termed "proarrhythmic response."¹⁻⁵ Although few would dispute that certain manifestations represent proarrhythmia, such as drug-induced long QT with polymorphic VT or VT occurring soon after the institution of therapy with type IC agents, criteria for proarrhythmic effects with regard to uniform VT are less clear. Some workers have used ambulatory monitoring, identifying an increase in frequency or types of spontaneous ventricular ectopy as proarrhythmic effects.⁶ However, the relation of increases in the frequency of asymptomatic spontaneous ectopy or nonsustained VT to the occurrence of sustained symptomatic arrhythmias is not clear. In addition, the relatively short peri-

ods of monitoring used in these studies may be associated with marked spontaneous variation in the frequency of spontaneous ectopy, clouding the interpretation of such changes.

Several reports have described alterations in the response to programmed stimulation, manifested by conversion of nonsustained or no VT into sustained VT after antiarrhythmic drugs.^{4,7,11} Rinkenberger et al⁷ reported conversion of nonsustained to sustained VT in 11 patients. However, 10 of the 11 had spontaneous ventricular fibrillation or sustained VT before study. These authors did not specify whether patients were receiving antiarrhythmic agents at the time of the spontaneous arrhythmia. The stimulation protocol used included only 2 ventricular extrastimuli. Such a protocol may fail to induce 25 to 40% of sustained tachyarrhythmia that would be induced by adding a third extrastimulus.¹⁴ If their patients fell into this group, initiation of sustained tachycardia after a drug when using this protocol would merely represent a decrease in the number of extrastimuli required to induce the tachycardia. Ruskin et al⁸ reported 6 patients who presented with cardiac arrest while receiving antiarrhythmic therapy. In 1 of these, the mechanism of cardiac arrest appeared likely to be secondary to a conduction abnormality induced by the drug, and in 1 patient no arrhythmia could be induced in the baseline state or after administration of quinidine. In 3 of the 4 remaining patients without any inducible arrhythmia during baseline study, only nonsustained tachycardias were induced after the drug, whereas in the fourth patient a sustained VT was induced after administration of quinidine. The report does not state whether the tachycardia induced was uniform or polymorphic. Bhandari et al¹¹ described a patient who developed spontaneous sustained uniform VT after administration of procainamide. In this patient, no arrhythmia was inducible in the baseline state, whereas the uniform sustained tachycardia was inducible after administration of procainamide.

Some workers classified as proarrhythmic effects a decrease in the number of extrastimuli required to induce sustained VT after antiarrhythmic drug administration.^{4,9} In our population of 80 patients with spontaneous sustained VT, we could not correlate this response with the patients' clinical presentation. These observations extend and confirm those reported recently by Kudenchuk et al¹⁵ in a smaller, heterogeneous group of patients.

The mechanisms underlying our observations are not clear. The increase in the cycle length of induced tachycardias, out of proportion to the measured increase in ventricular refractoriness after procainamide,

suggests that the predominant effect of procainamide is to cause slowing of conduction in the tachycardia circuit. Such slowing of conduction could facilitate conversion of nonsustained into sustained tachycardia, especially because cycle lengths of the tachycardias induced in the baseline state in group I were relatively short. Shen and Antzelevitch¹⁶ described an experimental model of reflected reentry that appears to exhibit behavior analogous to that which we observed. In their model, under conditions of mild conduction impairment in the ischemic gap, additional conduction slowing produced by the addition of quinidine facilitated reentry.

We cannot state with certainty whether the conversion of nonsustained to sustained VT after procainamide that we observed in the laboratory represents a true "proarrhythmic" effect. The correlation of clinical with laboratory events suggests that this may be the case. In any case, we believe this to be an important demonstration of the ability of an antiarrhythmic drug to convert a reentrant arrhythmia from a nonsustained to a sustained form.

Our observations suggest a limited role at present for the electrophysiology laboratory in recognizing the proarrhythmic effects of type IA agents in patients presenting with uniform sustained VT. Although clear-cut manifestations of proarrhythmic drug effects may occur (such as the spontaneous onset of VT during or after acute drug administration), they are rare. These conclusions should not be extended to other types of antiarrhythmic agents at this time, or to patient populations without a history of myocardial infarction. In addition, our results may not correspond to those obtained in a population presenting with cardiac arrest after myocardial infarction. We purposely chose to examine a population restricted to patients with electrocardiographically proven uniform sustained VT, because the spontaneous arrhythmia was well documented, in contrast to patients presenting with cardiac arrest.

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Effectiveness of Glibenclamide on Myocardial Ischemic Ventricular Arrhythmias in Non-Insulin-Dependent Diabetes Mellitus

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Glibenclamide, a hypoglycemic sulfonylurea, is a blocker of the adenosine triphosphatase-modulated potassium ion channels. The opening of these channels in the myocardial cells, induced by acute myocardial hypoxia, can be responsible for ischemic ventricular arrhythmias. To evaluate the antiarrhythmic effects of this drug 19 non-insulin-dependent diabetic patients were selected. They had coronary artery disease and evidence on Holter monitoring of ventricular premature complexes or nonsustained ventricular tachycardia, or both, induced by transient myocardial ischemia. In all patients, 24-hour electrocardiographic monitoring was performed to evaluate the number and duration of myocardial ischemic events, the frequency of ventricular premature complexes and nonsustained ventricular tachycardia per minute of ischemia and the percentage of ventricular premature complexes versus total ischemic beats. Selected patients were classified in 2 groups: group A (9 patients) received metformin (placebo) and group B (10 patients) was treated with glibenclamide. On the fourteenth day patients underwent 24-hour control monitoring. Then a crossover between the 2 groups was made and a new Holter monitoring sequence was performed at the end of the second phase. Results indicate that glibenclamide significantly ($p < 0.001$) reduced both the frequency of ventricular premature complexes and the episodes of nonsustained ventricular tachycardia during transient myocardial ischemia, but did not change the number and duration of acute myocardial ischemic attacks and did not reduce

the spontaneous ventricular arrhythmias. Thus, glibenclamide appears to have an antiarrhythmic effect in preventing ventricular arrhythmias induced by transient myocardial ischemia.

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Ventricular arrhythmias often occur during acute myocardial ischemia in patients with diabetes mellitus and coronary artery disease.¹⁻⁶ Electrophysiologic studies have shown that these arrhythmias are especially linked to an intracellular potassium ion (K^+) loss through adenosine triphosphatase (ATP)-modulated K^+ channels. The intracellular ATP concentration in normal cardiac cells is about 3 to 4 mM. Its reduction below 10% of this value, induced by acute myocardial hypoxia, can be responsible for a K^+ channel opening.⁷ The extracellular K^+ increase changes electrophysiologic properties of the myocardial fibers and could result in dispersion of the cellular recovery time, with the beginning of ventricular ectopic beats.^{8,9} Previous investigations reported that glibenclamide, a hypoglycemic sulfonylurea, is a potent blocker of these K^+ channels in pancreatic β cells, in skeletal muscle cells and in myocardial fibers.⁷⁻¹⁴ The aim of the present study was to evaluate the antiarrhythmic effectiveness of glibenclamide in non-insulin-dependent diabetes mellitus patients with coronary artery disease and Holter evidence of ventricular premature complexes or nonsustained ventricular tachycardia, or both, induced by transient myocardial ischemia.

METHODS

Patients: The study group consisted of 19 men, aged 42 to 63 years (mean \pm standard deviation 55 ± 6), affected by type II (non-insulin-dependent) diabetes mellitus and selected from 87 (22%) diabetic patients with coronary artery disease and no evidence of other cardiac disease. Seven had a history of myocardial infarction for >6 months before the study; 9 patients had effort angina and the remaining 3 had variant angina.

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TABLE I Holter Monitoring Reports

	Total Hours of Electrocardiography	Total Beats
Basal examination	22 ± 1	10,552 ± 10,733
Group A	22 ± 1	105,456 ± 10,023
First phase		
Group B	22 ± 1	106,880 ± 11,032
Group A	22 ± 1	106,357 ± 10,129
Second phase		
Group B	22 ± 1	106,421 ± 10,134

Mean values ± standard deviation of total hours of Holter monitoring and of total beats recorded in basal conditions and after 2 phases of treatment in groups A and B. Differences between these values were not significant.
First phase = group A (glibenclamide); group B (metformin).
Second phase = group A (metformin); group B (glibenclamide).

Patient selection was based on the 24-hour Holter recording of ventricular arrhythmias induced by transient myocardial ischemia. Before the study, all patients were treated with nitrates (from 40 to 60 mg/day) and an oral hypoglycemic drug different from glibenclamide.

Criteria of acute myocardial ischemia: During Holter monitoring, the diagnosis of transient myocardial ischemia was obtained at a J-point depression or elevation of ≥ 2 mm, with ST-segment displacement lasting 0.08 second from the J point. In addition, the angle of the ST segment was also measured relative to the isoelectric line. This computation was made between point 0.02 second and point 0.08 second from the J point. The J point and ST-segment displacements were judged significant for transient myocardial ischemia when their duration lasted for ≥ 10 consecutive beats. In all selected patients, ventricular premature complexes and nonsustained ventricular tachycardia were defined as ischemic arrhythmias when they occurred immediately after the appearance of the J point and ST displacements mentioned before.¹⁵ In addition, in the 9 patients with effort angina and in the 7 with previous myocardial infarction the ischemic cause of ventricular arrhythmias was also confirmed by findings obtained during the treadmill stress test. All Holter examinations were recorded with a 2-channel I.C.R. 1201 series using modified lead II and V₅ systems.

Study protocol: After baseline Holter evaluation, all patients were classified randomly into 2 groups: group A (9 patients) treated with metformin (1,000 mg in 2 divided doses orally), used as a placebo and Group B (10 patients) treated with glibenclamide (10 mg in 2 divided doses). This treatment lasted 2 weeks (first phase). During the fourteenth day the 2 groups of patients underwent new 24-hour Holter monitoring. Then, metformin was substituted with glibenclamide in group A and glibenclamide with metformin in group B. This therapy lasted for another 2 weeks (second phase).

At the end of this period a third 24-hour Holter recording was performed. The mean value of fasting plasma glucose levels was evaluated in all patients, both during basal conditions and after randomization, before and after crossover.

Statistical analysis: Differences in the values of plasma glucose levels were evaluated by the Student's *t* test for unpaired data and a *p* value <0.05 was considered significant. Holter results included a calculation of: (1) total hours of Holter monitoring; (2) number of total beats during Holter recording; (3) minutes of transient myocardial ischemia in 24 hours; (4) logarithm of the frequency of isolated ventricular premature complexes per minute of acute ischemia and per hour during nonischemic periods; (5) percentage of premature ventricular complexes per number of ischemic beats; and (6) logarithm of the number of nonsustained ventricular tachycardias per minute of transient ischemia. Logarithms of ventricular premature complexes and episodes of nonsustained ventricular tachycardia were used in place of absolute frequency to stabilize the variance and to normalize the distribution of these events.¹⁶ Mean values of Holter parameters obtained in basal conditions and after metformin and glibenclamide treatments before and after crossover were compared. Statistical analysis was performed using Student's *t* test for unpaired data; a *p* value <0.05 was considered significant.

RESULTS

Plasma glucose levels: The mean value of fasting plasma glucose baseline levels was 8.45 ± 0.92 mOsmol/ml. At the end of the first phase, this value was 8.16 ± 1.07 mOsmol/ml in patients in group A (metformin) and 8.22 ± 1.09 in those in group B (glibenclamide). After the second phase, mean glucose levels were 8.42 ± 0.77 mOsmol/ml in group A (glibenclamide) and 8.45 ± 0.94 mOsmol/ml in group B (metformin). Differences between the baseline glucose levels and the values found in the placebo and glibenclamide groups were not significant both before and after crossover.

Holter reports: Table I lists mean values \pm standard deviations, with statistical significance of the total hours of Holter monitoring and the number of total beats recorded in basal conditions and in 2 groups before and after crossover. The mean duration of transient myocardial ischemia was 11 ± 4 minutes per 24 hours during the basal recording. At the end of the first phase, acute ischemia lasting a mean of 11 ± 4 minutes was found in patients taking placebo (group A), whereas its duration was 11 ± 3 minutes in patients taking gliben-

clamide (group B). After the second phase in the diabetic patients in group A (who received glibenclamide), a mean of 11 ± 4 minutes of acute myocardial ischemia was found; in those in group B (placebo) a mean of 11 ± 3 minutes was recorded. Differences in the duration of transient myocardial ischemia found during the baseline recording and those obtained in patients in groups A and B before and after crossover were not significant (Figure 1).

Ventricular arrhythmias: The logarithm of isolated ventricular premature complexes per minute of ischemia taken during the basal examination was 1.3 ± 0.12 . After the first treatment, this value was 1.35 ± 0.15 in the diabetic patients treated with metformin (group A) and 0.21 ± 0.36 in those who received glibenclamide (group B). This last reduction was statistically significant ($p < 0.001$). At the end of the second period, the value of this logarithm was 0.22 ± 0.35 in the glibenclamide group. The difference in respect to the basal value was significant ($p < 0.001$). On the con-

trary, no difference was found when comparing the basal value with that in the placebo group (1.34 ± 0.11) (Figure 2). Differences between the mean values of isolated ventricular premature complexes per hour of nonischemic periods found during the basal examination and in 2 groups after the 2 phases were not significant. The mean percentage of ventricular premature complexes per number of ischemic beats found during basal examination was $28 \pm 8\%$. At the end of the first 2 weeks this value remained unchanged in the metformin group ($28 \pm 7\%$). In contrast, it was significantly smaller ($p < 0.001$; $2.6 \pm 2\%$) in patients treated with glibenclamide. The same results were obtained in the glibenclamide and metformin groups after the crossover (Figure 3). Finally, the logarithmic number of episodes of nonsustained ventricular tachycardia per minute of ischemia at the basal level was 0.24 ± 0.16 . After the first phase no significant difference was found in the patients in group A (0.25 ± 0.09), whereas this value was significantly smaller (0.003 ± 0.004) in diabetic

FIGURE 1. Duration in minutes of transient myocardial ischemia during basal electrocardiographic 24-hour examination in the 2 groups (placebo and glibenclamide) before and after crossover.

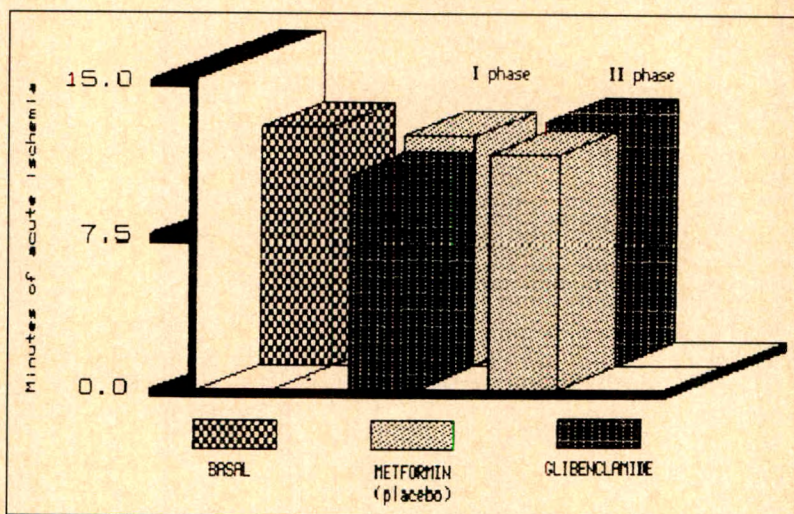
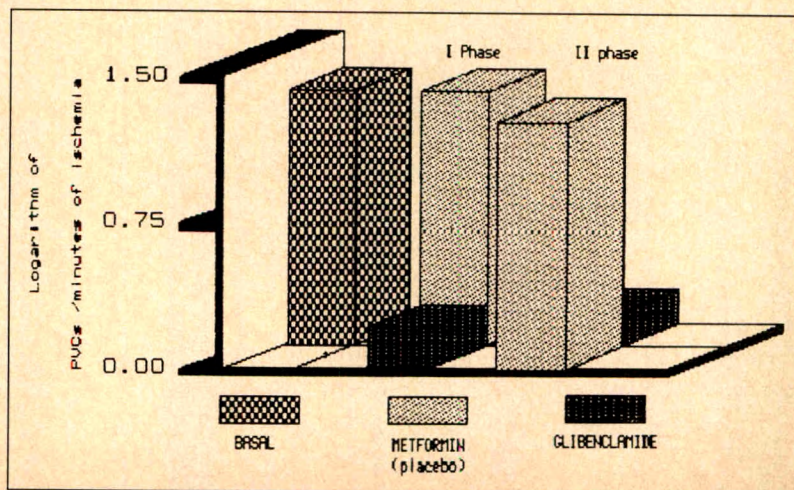


FIGURE 2. Behavior of the logarithm of ventricular premature complexes (PVCs) frequency per minute of acute ischemia in basal conditions and after 2 phases of treatment with metformin in the placebo and glibenclamide groups.



patients treated with glibenclamide. After the cross-over, patients in group A (who received glibenclamide) also had a significant ($p < 0.001$) reduction (0.004 ± 0.002) in the logarithm of this parameter (Figure 4).

DISCUSSION

Mechanism of ischemic ventricular arrhythmias:

The ischemic cause of ventricular premature complexes found in our selected patients is shown by their occurrence just after the appearance of the J point and ST-segment displacements on Holter recording. An increased extracellular K^+ concentration is a major determinant of these arrhythmias.^{17,18} Harris et al⁸ were among the first to identify an increased extracellular K^+ concentration as a major determinant of ischemic tachyarrhythmias. The importance of the increase in extracellular K^+ concentration with respect to electrophysiologic changes during ischemia was also recently demonstrated by Coronel et al.¹⁹ They found that during acute myocardial ischemia, K^+ flows from the isch-

emic zone into the normal zone. The marked inhomogeneity in K^+ concentration in the border zone suggests inhomogeneity in electrophysiologic properties that may be of importance in the genesis of reentrant activity. The reduction of K^+ concentration in myocardial ischemic cells is due to the opening of specific ATP-regulated K^+ channels as a direct consequence of a severe cardiac hypoxia.⁷ The intracellular ATP concentration in normal cardiac cells has been reported to be 3 to 4 mM.⁷ Acute hypoxia induces a decreased activity of the mitochondrial respiratory chain, responsible for the reduction of high-energy phosphate levels. Experimental data reported that these channels are opened when the intracellular ATP concentration is reduced from 0.05 to 1 mM.⁷ This intracellular ATP depletion during acute ischemia causes an intracellular K^+ loss with consequent extracellular K^+ increase. Moreover, other cations, such as magnesium ion (Mg^{++}) and sodium ion (Na^+) physiologically present in the cytoplasm, are also implicated in the activity of these channels. In fact,

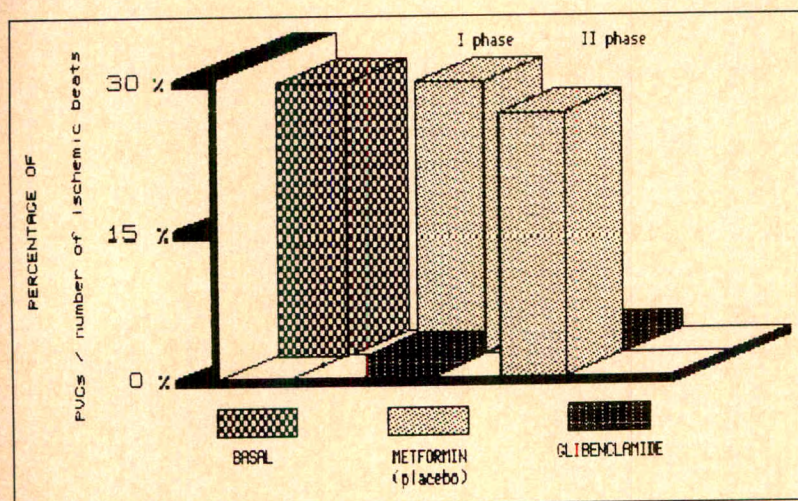


FIGURE 3. Percentage of ventricular premature complexes (PVCs) per number of ischemic beats found during baseline evaluation and after 2 periods of therapy in 2 randomized groups.

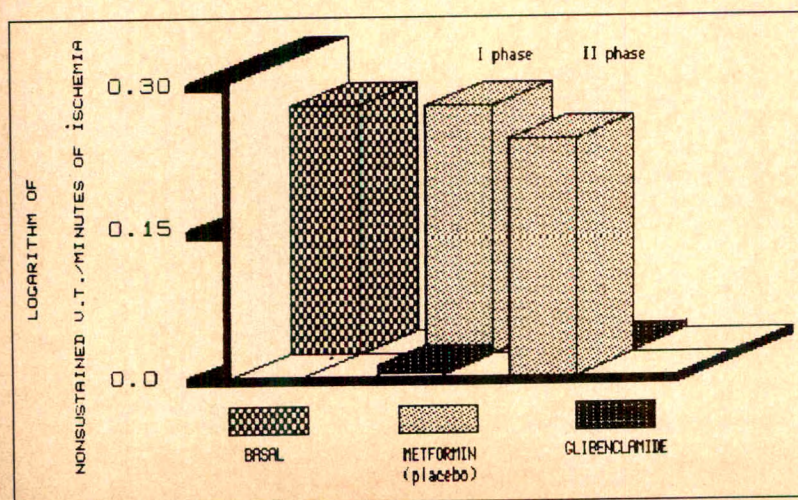


FIGURE 4. Logarithms of the episodes of nonsustained ventricular tachycardia (V.T.) per minute of ischemia recorded during basal conditions and in 2 groups of treated patients before and after cross-over.

during ischemia in guinea pig ventricular cells, Horie et al²⁰ observed that, when the open probability of ATP-sensitive K⁺ channels is increased, internal free Mg⁺⁺ and Na⁺ levels will be elevated as a result of the release of Mg⁺⁺ bound to ATP and the accumulation of Na⁺ due to disturbed Na⁺-K⁺ pump activity.

Mechanism of glibenclamide action: Several reports^{10,12,21,22} described the antidiabetic sulfonylurea glibenclamide as a potent blocker of these ATP-modulated K⁺ channels. On the pancreatic β cells, the slow wave of depolarization that follows glucose application is due to closure of a K⁺ channel that is regulated by intracellular ATP. Like glucose, sulfonylureas induce electrical activity in pancreatic islets and the 2 pathways of glucose and sulfonylurea-induced insulin release converge at the level of the ATP-regulated conductance. This property of glibenclamide has also been found in mammalian heart cells.⁷ In a recent study, Kantor et al¹⁴ demonstrated that glibenclamide significantly reduces ischemic arrhythmias in rat hearts with a mechanism mediated by decreasing K⁺ loss from ischemic tissue. This effect was not dependent on the direct action of the glycolytic pathway; no changes were found in glycolytic or lactate production.¹⁴ On the basis of these reports, we evaluated the effectiveness of glibenclamide on acute ischemic ventricular arrhythmias in patients with non-insulin-dependent diabetes mellitus and coronary artery disease. After glibenclamide therapy, the rate of acute ischemic events remained unchanged, but the frequency of ventricular premature complexes and nonsustained ventricular tachycardia per minute of acute ischemia significantly decreased.

Clinical implications: Our results suggest that glibenclamide is not an antiischemic drug, but it has an antiarrhythmic effect that is not dependent on the reducing action of glucose. Moreover, this effect was present in patients with only acute ischemic arrhythmias. In fact, ventricular premature complexes and nonsustained ventricular tachycardia during nonischemic periods were unchanged after glibenclamide treatment.

Thus, despite the small population studied, the results obtained suggest that glibenclamide appears to have an antiarrhythmic effect on the multiple ventricular ectopic beats induced by transient myocardial ischemic events in patients with non-insulin-dependent diabetes mellitus. Nevertheless, further and more widespread studies are required to confirm these results.

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Incremental Prognostic Value of Exercise Hemodynamic Variables in Chronic Congestive Heart Failure Secondary to Coronary Artery Disease or to Dilated Cardiomyopathy

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To determine the prognostic value of hemodynamic variables at rest and during exercise, 49 patients with chronic congestive heart failure undergoing hemodynamic evaluation at rest and during symptom-limited exercise were followed for 1 year. One-year mortality rate was 33%. On univariate analysis, nonsurvivors differed significantly from survivors in pulmonary arterial wedge pressure at rest (22 ± 10 vs 15 ± 10 mm Hg; $p = 0.01$) and during exercise (32 ± 9 vs 24 ± 9 mm Hg; $p = 0.003$), stroke work index at rest (19 ± 6 vs 25 ± 9 g-m/m²; $p = 0.03$) and during exercise (20 ± 7 vs 32 ± 14 g-m/m²; $p = 0.001$) and exercise-induced increment in stroke work index (0.5 ± 0.4 vs 7 ± 8 g-m/m²; $p = 0.004$), but not with respect to left ventricular ejection fraction, exercise duration, peak oxygen consumption or peak left ventricular hydraulic power. Patients with a peak exercise stroke work index <20 g-m/m² had a 66% mortality rate compared with a mortality rate of 13% in patients with a peak exercise stroke work index >20 g-m/m² ($p = 0.0001$). Multiple logistic regression analysis identified pulmonary arterial wedge pressure at rest and peak exercise stroke work index as the only independent predictors of mortality. A receiver-operating characteristic curve analysis revealed that peak exercise stroke work index provided significant incremental prognostic information over the resting hemodynamic variables.

These data suggest that among patients with chronic congestive heart failure, a subset of patients with a very high 1-year mortality may be identified using hemodynamic evaluation at rest and during exercise and this information may be useful when selecting patients for cardiac transplantation.

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Hemodynamic variables measured at rest and during exercise have been widely used in patients with chronic congestive heart failure (CHF) to define pathophysiology,¹⁻⁴ and to assess the effects of drug therapy.⁵⁻⁹ However, in determining prognosis, most studies have used resting rather than exercise hemodynamic variables.¹⁰⁻¹⁴ Hemodynamic variables obtained at peak exercise have potential advantages over the resting variables in that they may more closely reflect cardiac functional reserve and thus be expected to better predict survival.¹⁵ This has already been shown for a group of patients with CHF in which inotropic stimulation was used to achieve maximal pumping capacity.¹⁶ Although disparate responses in cardiac pump function on graded exercise have been reported in patients with chronic CHF, the prognostic significance of these findings has not been adequately addressed.^{2,4} In this study, the prognostic importance of resting and exercise hemodynamic and gas exchange variables has been evaluated in patients with chronic CHF using univariate and multivariate analysis.

METHODS

Patients: The study consisted of 49 patients with chronic CHF referred to this institution for functional evaluation or optimization of therapy. All patients had symptoms of CHF for at least 1 year and none had an episode of acute pulmonary edema within 1 month of the study. The mean age \pm standard deviation was 63

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\pm 11 years and 39 (80%) were men. Nine patients (18%) had New York Heart Association class II, 28 patients (57%) had class III and 12 (25%) had class IV heart failure. The underlying basis for chronic CHF was coronary artery disease in 36 (74%) and dilated cardiomyopathy in 13 (26%) patients.

Assessment of hemodynamic variables and gas exchange at rest and during exercise: The detailed protocol for resting and exercise measurements has been described elsewhere.¹⁷ Briefly, a pulmonary artery balloon flotation catheter was inserted percutaneously in all patients and positioned in the pulmonary artery under hemodynamic and fluoroscopic guidance. Intracardiac pressures were measured with the transducer placed at the level of the fourth intercostal space in the midaxillary line. Cardiac output was determined in triplicate using the thermodilution technique. Arterial blood pressure was measured from an indwelling cannula in the radial artery. Heart rate and rhythm were recorded from an electrocardiographic monitor. Expired gas was obtained for measurements of ventilation, oxygen uptake and carbon dioxide output using a pneumotachograph and mass spectrometer. Exercise was performed on a weight flywheel upright bicycle ergometer. The exercise protocol consisted of 3-minute stages beginning with unloaded pedaling and the work load was increased by 25 W at each stage. Patients exercised to their symptom-limited maximum. All patients with coronary artery disease had undergone prior stress testing and none had evidence of significant reversible ischemia. Hemodynamic measurements were made at rest and again at peak exercise. Stroke work and cardiac indexes were derived using standard formulas. Left ventricular hydraulic power output (power) was calculated as: mean arterial blood pressure \times mean right atrial pressure \times cardiac output \times 0.00222 W. Stroke work index and left ventricular hydraulic power were used as indexes of the pumping capacity of the heart at rest and at peak exercise.

Left ventricular ejection fraction: In 40 of the 49 patients, left ventricular ejection fraction was measured by equilibrium-gated radionuclide blood pool scintigraphy.¹⁸

Follow-up: One-year follow-up was conducted on all patients by contacting primary care physicians or family members or by contacting the patient directly. Death was ascribed to pump failure when death was due to intractable heart failure or to sudden death if it occurred in the presence of stable or improving heart failure and within 10 minutes of the onset of new symptoms.

Treatment: All patients received digoxin and diuretics as part of their treatment. In addition, 69% re-

ceived vasodilators (nitrates, converting enzyme inhibitors, direct acting vasodilators). Cardioactive medication was given on the morning of the study, a minimum of 2 hours before its commencement.

Statistics: All data are expressed as mean \pm standard deviation. A paired or unpaired *t* test was used to compare the means of continuous data, whereas chi-square or Mann-Whitney tests were used to compare categorical variables. A *p* value <0.05 was considered significant.

Assessment of incremental information: Maximum likelihood logistic regression was used to identify predictors of cardiac mortality at 1 year after the hemodynamic assessment. The commercially available statistical package was used for this analysis.¹⁹ This analysis was performed in 2 steps, in the first of which the significant predictors among the resting hemodynamic variables (mean arterial pressure, heart rate, pulmonary arterial wedge pressure, oxygen uptake, stroke work index) were determined. At step 2, a second model was developed in which the peak exercise values of these hemodynamic variables were added to the model developed at step 1. The *p* value to enter and remove variables was 0.1 and 0.15, respectively.

Incremental information from the addition of the exercise data was indicated by an improvement in the likelihood ratio of the second model. This was further investigated by comparing the discriminant accuracy of the models at each step. Discriminant accuracy was measured by determining the area under the respective receiver-operating characteristic curve. These curves were constructed using the methods described by Hanley and McNeill^{20,21} on the basis of the predicted logistic probabilities of individual patients.

RESULTS

Survival: No patients were lost to follow-up. Sixteen patients (33%) died within a year of hemodynamic evaluation. All deaths were attributable to CHF with 9 (56%) resulting from intractable pump failure and 7 patients (44%) dying suddenly. Table I summarizes the baseline clinical characteristics of the patient cohort. Survivors did not differ significantly from nonsurvivors with respect to age, gender, New York Heart Association class, cause of CHF, history of prior myocardial infarction, left ventricular ejection fraction or drug therapy.

Hemodynamic variables and oxygen uptake at rest: Resting hemodynamic variables and oxygen uptake are presented for survivors, nonsurvivors and for the entire cohort in Table I. Pulmonary arterial wedge pressure was significantly higher and stroke work index was significantly lower in nonsurvivors than in survivors. Other

hemodynamic variables and the resting oxygen uptake did not differ between survivors and nonsurvivors.

Hemodynamic variables and oxygen uptake at peak exercise: The hemodynamic and oxygen uptake data at peak exercise are listed in Table I for survivors, nonsurvivors and the entire cohort. As in the case of resting variables, nonsurvivors had a significantly higher pulmonary arterial wedge pressure and a lower stroke work index than survivors. In addition, stroke volume

index at peak exercise was also significantly lower in nonsurvivors than survivors. There was no significant difference in either the exercise duration or the peak oxygen uptake between survivors and nonsurvivors. None of the patients developed symptoms or electrocardiographic evidence of ischemia during exercise.

Exercise-induced changes in hemodynamic variables: Exercise-induced changes in hemodynamic variables are listed in Table II. Increments in cardiac,

TABLE I Clinical Characteristics, Exercise and Hemodynamic Data

	All	Alive	Dead
No. of patients	49	33	16
Age (years)	62 ± 11	62 ± 11	64 ± 10
Sex (men)	39 (80%)	26 (79%)	13 (81%)
New York Heart Association class			
II	9 (18%)	7 (21%)	2 (13%)
III	28 (57%)	19 (58%)	9 (56%)
IV	12 (25%)	7 (21%)	5 (31%)
Coronary artery disease (%)	36 (74%)	24 (73%)	12 (75%)
Prior myocardial infarction	33 (68%)	22 (67%)	11 (69%)
Left ventricular ejection fraction (%)	23 ± 9	24 ± 9	19 ± 9
Prior coronary bypass grafting (%)	17 (35%)	14 (42%)	3 (19%)
Vasodilators	34 (69%)	24 (73%)	10 (63%)
Heart rate (beats/min)	Rest 89 ± 15	87 ± 16	93 ± 12
	Exercise 112 ± 21	109 ± 24	117 ± 11
Mean arterial pressure (mm Hg)	Rest 88 ± 13	90 ± 13	85 ± 12
	Exercise 98 ± 19	100 ± 20	92 ± 15
Pulmonary arterial wedge pressure (mm Hg)	Rest 17 ± 10	15 ± 10	22 ± 10*
	Exercise 27 ± 9	24 ± 9	32 ± 9†
Right atrial pressure (mm Hg)	Rest 4 ± 4	4 ± 4	5 ± 5
	Exercise 11 ± 7	10 ± 6	13 ± 7
Cardiac index (liters/min/m ²)	Rest 2.0 ± 0.4	2.0 ± 0.4	2.0 ± 0.5
	Exercise 3.1 ± 1.0	3.2 ± 1.1	2.8 ± 0.7
Stroke volume index (ml/m ²)	Rest 23 ± 6	24 ± 6	22 ± 5
	Exercise 28 ± 9	30 ± 9	24 ± 6
Systemic vascular resistance (s-cm ⁻⁵)	Rest 1,936 ± 530	1,978 ± 486	1,847 ± 620
	Exercise 1,371 ± 590	1,366 ± 573	1,381 ± 644
Oxygen uptake (ml/min)	Rest 257 ± 57	255 ± 55	263 ± 61
	Exercise 675 ± 216	703 ± 221	616 ± 200
Stroke work index (g-m/m ²)	Rest 23 ± 9	25 ± 9	19 ± 6†
	Exercise 28 ± 13	32 ± 14	20 ± 7*
Power (W)	Rest 0.7 ± 0.2	0.7 ± 0.2	0.7 ± 0.2
	Exercise 1.1 ± 0.5	1.2 ± 0.6	0.9 ± 0.3
Exercise duration (min)	8 ± 2	8 ± 2	7 ± 2
Peak work load (W)	38 ± 19	39 ± 21	37 ± 14

p value between survivors and nonsurvivors: * p < 0.01; † p < 0.05.

TABLE II Change in Hemodynamic Parameters from Rest to Peak Exercise

	All	Alive	Dead	p Value
No. of patients	49	33	16	
Heart rate (beats/min)	23 ± 16	22 ± 19	25 ± 11	NS
Mean arterial pressure (mm Hg)	9 ± 11	10 ± 12	8 ± 9	NS
Pulmonary arterial wedge pressure (mm Hg)	9 ± 7	9 ± 7	10 ± 7	NS
Right atrial pressure (mm Hg)	7 ± 5	6 ± 4	8 ± 5	NS
Cardiac index (liters/min/m ²)	1.1 ± 0.8	1.2 ± 0.9	0.8 ± 0.4	0.05
Stroke volume index (ml/m ²)	5 ± 7	7 ± 7	2 ± 5	0.016
Systemic vascular resistance (s-cm ⁻⁵)	-565 ± 385	-613 ± 395	-466 ± 354	NS
Oxygen uptake (ml/min)	228 ± 109	245 ± 114	192 ± 90	NS
Stroke work index (g-m/m ²)	5 ± 8	7 ± 8	0.5 ± 4	0.004
Power (W)	0.4 ± 0.4	0.5 ± 0.5	0.2 ± 0.2	0.04

NS = not significant.

stroke volume and stroke work indexes and left ventricular hydraulic power were significantly less for nonsurvivors than survivors. The increase in pulmonary arterial wedge pressure was comparable among survivors and nonsurvivors (Figure 1). Survivors increased cardiac index during exercise by increasing heart rate and stroke volume, whereas in nonsurvivors the small increase in cardiac index was due to an increase in heart rate only.

Relation of peak stroke work index to mortality:

The mortality was significantly higher in patients who achieved a peak stroke work index <20 g-m/m² compared to those whose peak exercise stroke work index exceeded 20 g-m/m² (66 vs 13%; $p < 0.0001$). Patients who were unable to increase stroke work index during exercise by >1 g-m/m² also had a significantly higher mortality than those who increased stroke work index by >1 g-m/m² (55 vs 17%; $p < 0.006$) (Table III). Three of 4 deaths in patients with a peak exercise stroke work index >20 g-m/m² were sudden. The mortality was not significantly different between patients achieving a peak left ventricular hydraulic power value of >1 or <1 W.

Incremental information: At step 1, pulmonary arterial wedge pressure was the only significant predictor of mortality among the resting hemodynamic variables. The logistic regression model based on resting pulmonary capillary wedge pressure had a $71 \pm 8\%$ discriminant accuracy in predicting 1-year survival. At step 2, a peak stroke work index added significantly to the information contained in resting pulmonary arterial wedge pressure as indicated by an increase in the chi-square value ($p < 0.001$). Discriminant accuracy improved at this step to $79 \pm 7\%$ on addition of the peak exercise stroke work index. The receiver-operating characteristic curves for the resting and exercise data are illustrated in Figure 2. Additional information from the exercise data was seen over a wide range of specificities and sensitivities, with the greatest additional information being seen at 20 to 70% sensitivity and 50 to 90% specificity.

DISCUSSION

Main findings: This prospective study of ambulatory patients with chronic CHF shows that hemodynamic measurements at peak exercise provide important prognostic information with respect to 1-year mortality which is a significant addition to information provided by resting hemodynamic variables. Specifically, inability to achieve a peak stroke work index of >20 or <1 g-m/m² increment in stroke work index at peak exercise identified patients with a three- to fivefold higher mortality compared with remaining patients. Furthermore,

TABLE III Stroke Work, Peak Power and Relation to Mortality

		Alive	Dead	All	p Value
Change in stroke work index	<1 g-m/m ²	9	11	20	<0.006
	>1 g-m/m ²	24	5	29	
Peak stroke work index	<20 g-m/m ²	6	12	18	<0.0001
	>20 g-m/m ²	27	4	31	
Peak power	<1 W	14	10	24	NS
	>1 W	19	6	25	

NS = not significant.

other descriptors of overall pump function such as left ventricular ejection fraction, New York Heart Association class, peak hydraulic power, exercise duration, and resting and peak oxygen uptake failed to discriminate survivors from nonsurvivors. The overall 1-year mortality rate of 33% observed in this cohort of patients is consistent with previously reported mortality figures in patients with chronic CHF.^{12,22,23}

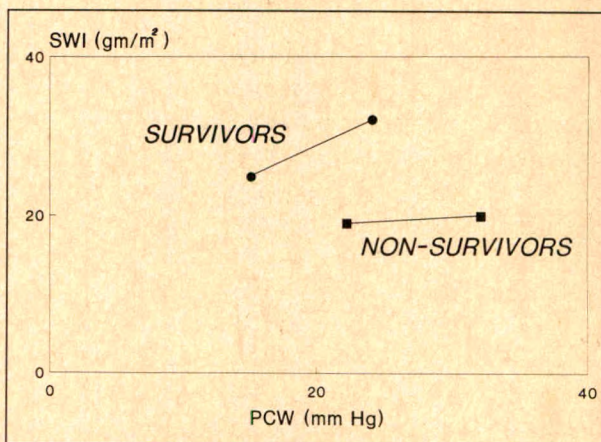


FIGURE 1. The changes in stroke work index (SWI) and pulmonary capillary wedge pressure (PCW) from rest to exercise are contrasted between survivors and nonsurvivors.

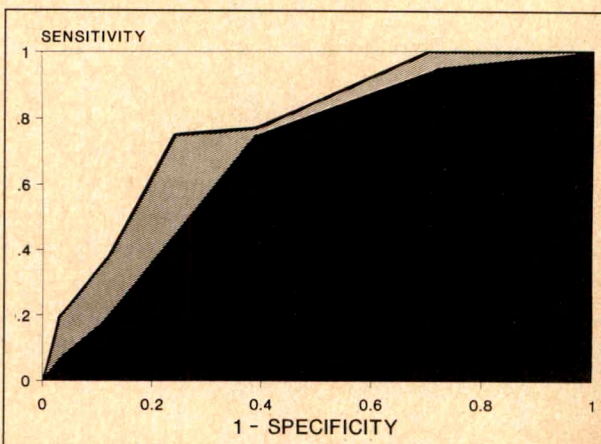


FIGURE 2. The receiver-operating characteristic curve for resting hemodynamic data is illustrated by the solid area. The additional information provided by exercise hemodynamic data is illustrated by the hatched area.

Comparison with previous reports: Hemodynamic measurements at rest have been shown to predict prognosis in patients with CHF. In our study, pulmonary arterial wedge pressure and stroke work index proved to be the univariate predictors of outcome among the resting hemodynamic parameters. Previous studies have also indicated that both these resting parameters are prognostically useful in patients with chronic CHF.^{12,14,22}

The prognostic significance of the hemodynamic measurements performed after pharmacologic interventions has been described, but little information is available concerning the prognostic use of hemodynamic measurements obtained at peak exercise. Massie et al²² showed that pulmonary arterial wedge pressure and stroke work index after starting vasodilator therapy was predictive of survival, but that study did not indicate whether the drug intervention provided incremental information concerning prognosis beyond that obtained before treatment.

Tan¹⁶ determined maximal cardiac pump function by means of inotropic stimulation of the heart with dobutamine. In 2 groups of patients, one with CHF,¹⁶ the other with cardiogenic shock,²⁴ he has shown that peak stroke work index and peak left ventricular hydraulic power are important determinants of 1-year survival. In our study, although peak stroke work index was a powerful predictor of 1-year survival, we did not find that a peak hydraulic power value of 1 W accurately discriminated survivors from nonsurvivors. A number of factors could explain the discrepant results with regard to the prognostic ability of peak left ventricular hydraulic power in our study compared with those of Tan. First, the patients studied by Tan tended to be more acutely ill than those in our study. Second, peak hydraulic power obtained by infusing dobutamine may not be analogous to that determined at peak exercise. Mean arterial and right atrial pressures that are an integral part of the hydraulic power computation might be expected to move in opposite directions with dobutamine compared with results during exercise. Thus, arterial pressure may decrease during exercise in patients with CHF, whereas right atrial pressure tends to increase. Dobutamine is more likely to increase blood pressure while lowering right atrial pressure. However, a recent study compared peak left ventricular hydraulic power and stroke work index determined by either maximal exercise or dobutamine infusion and found them similar.²⁵

Previous studies^{2,4} have examined the change in stroke work during exercise in patients with CHF. In both of these studies, 2 groups of patients were described based on the response of stroke work to exercise. In 1 group of patients, stroke work increased significantly during exercise (the normal response²⁶⁻²⁸); in

the other, no increase or a small decrease in stroke work was reported. Neither of these studies was of sufficient size to determine prognostic implications. The findings in the present study suggest that a failure to increase stroke work during exercise is associated with a substantially higher short-term mortality.

We did not find left ventricular ejection fraction to be a useful prognostic factor in the estimation of 1-year survival in this cohort of patients. Prior studies^{29,30} have indicated similar results, although left ventricular ejection fraction has been shown to be prognostically useful in patients with dilated cardiomyopathy.¹⁰ The relatively poor prognostic ability of left ventricular ejection fraction seen in this study probably relates to the relatively narrow range of resting ventricular function seen in this group compared with, e.g., survivors of myocardial infarction. In the latter group, a wide range of ventricular function is seen, and consequently resting indexes of ventricular function are of greater prognostic value. In patients with severe left ventricular dysfunction at rest, the determination of peak cardiac pump function and cardiac pumping reserve provide a spectrum of cardiac function that is prognostically powerful.

Although we found that the hemodynamic derangements as a result of exercising were of prognostic significance, neither duration of exercise nor oxygen uptake during exercise were significantly different among survivors and nonsurvivors. This is somewhat surprising given the reduced pumping capacity of the heart and the higher wedge pressure in the nonsurvivors. Previous reports²⁹ have indicated only a relatively loose correlation between exercise capacity and prognosis in heart failure.

Clinical implications: Our study suggests that information concerning the maximal pumping capacity and pumping reserve of the heart is prognostically important in patients with moderate to severe CHF. This is a group of patients who might be considered candidates for therapeutic interventions such as cardiac transplantation. As resources for transplantation are limited, it is important to select those at highest risk of early mortality for urgent intervention. We have found that the information available from exercise hemodynamics may be useful in stratifying patients with severe left ventricular dysfunction. In particular, we have found that patients with a low peak stroke work index during exercise or a stroke work index that did not increase during exercise have a very high 1-year mortality. These patients may therefore be considered for early cardiac transplantation.

Maximal cardiac capacity and cardiac reserve may be determined with inotropic stimulation or maximal symptom-limited exercise testing. Exercise has the ad-

vantage of being physiologic and in providing additional information such as exercise capacity and oxygen uptake, which can be used to assess a patient's response to treatment more accurately. Inotropic infusion has the advantage of being applicable in very ill patients who are incapable of exercise. Therefore, the appropriate method to determine maximal cardiac capacity in an individual patient should be determined by the clinical situation.

Our findings also indicate that, although a severely impaired cardiac pump function as indicated by exercise hemodynamic measurements is highly predictive of early mortality from pump failure, it is less predictive of sudden death in these patients. Sudden death accounts for up to 50% of all deaths in chronic CHF.^{22,23,31} Improved methods of defining those at risk of sudden death in this population are also required.

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Short- and Long-Term Results of Catheter Balloon Percutaneous Transvenous Mitral Commissurotomy

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Percutaneous transvenous mitral commissurotomy (PTMC) was performed in 219 patients with symptomatic, severe rheumatic mitral stenosis. There were 59 men and 160 women, aged 19 to 76 years (mean 43). Pliable, noncalcified valves were present in 139 (group 1), and calcified valves or severe mitral subvalvular lesions, or both, in 80 patients (group 2). Atrial fibrillation was present in 133 patients (61%) and 1+ or 2+ mitral regurgitation in 59 (27%). Technical failure occurred with 3 patients in our early experience. There was no cardiac tamponade or emergency surgery. The only in-hospital death occurred 3 days after the procedure in a group 2 premonitory patient in whom last-resort PTMC created 3+ mitral regurgitation. Mitral regurgitation appeared or increased in 72 patients (33%); 3+ mitral regurgitation resulted in 12 patients (6%). There were 3 systemic embolisms. Atrial left-to-right shunts measured by oximetry developed in 33 patients (15%). Immediately after PTMC, there were significantly reduced ($p = 0.0001$) left atrial pressure (24.2 ± 5.6 to 15.1 ± 5.1 mm Hg), mean pulmonary artery pressure (39.7 ± 13.0 to 30.6 ± 10.9 mm Hg) and mitral valve gradient (13.0 ± 5.1 to 5.7 ± 2.6 mm Hg). Mitral valve area increased from 1.0 ± 0.3 to 2.0 ± 0.7 cm² ($p = 0.0001$) and cardiac output from 4.4 ± 1.4 to 4.7 ± 1.2 liters/min ($p < 0.01$). The results mirrored clinical improvements in 209 patients (97%). Multivariate analysis showed an echo score >8 , and val-

vular calcification and severe subvalvular lesions as independent predictors for suboptimal hemodynamic results. The cardiovascular event-free survival rate for group 1 was 100% up to 42 months; that for group 2 was 91% at 12 months, and held at 76% from 24 to 31 months. PTMC is safe, achieves good immediate and long-term results and is the procedure of choice in selected patients with mitral stenosis.

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In 1984, a novel catheter intervention technique using a size-adjustable, self-positioning balloon catheter was introduced by Inoue et al¹ as a promising therapeutic alternative for surgical treatment of patients with severe mitral stenosis. Because the fused mitral commissures are split with a balloon catheter inserted percutaneously through the femoral vein after transseptal catheterization, the method was termed percutaneous transvenous mitral commissurotomy (PTMC). Extensive clinical trials in the Far East have established the effectiveness and safety of PTMC in well selected patients.²⁻⁵ However, reports of long-term effects of the procedure are few.⁵ In this communication, we present immediate outcomes and long-term results of PTMC performed by a single operator at a single institution in a large number of patients with severe rheumatic mitral stenosis.

METHODS

Patients: From January 1987 to December 1989, 219 patients with symptomatic, severe rheumatic mitral stenosis underwent PTMC. Patient selection was initially restricted to those with pliable, noncalcified mitral valves and without severe mitral subvalvular lesions. After the first 50 cases, the criteria were broadened to include patients with calcified mitral valves (as seen under fluoroscopy) and severe mitral subvalvular lesions.

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The latter were determined by 2-dimensional echocardiographic findings of severe thickening and shortening of chordal structures⁶ and by angiographic compression signs on the inflated balloon (Figure 1). Patients with angiocardiographic findings of severe mitral regurgitation ($\geq 3+$ by criteria of Sellers et al⁷) and left atrial thrombus on transthoracic 2-dimensional echocardiography were considered contraindicated and excluded from the study.

The patient pool comprised 59 men and 160 women, aged 19 to 76 years (mean 43), including 100 patients reported previously.³ One hundred thirty-nine patients with pliable, noncalcified valves were designated as group 1. Eighty patients, including 42 with calcified valves, 24 with severe subvalvular lesions and 14 with both, constituted group 2. The mean age was 39 ± 11 for group 1 and 48 ± 13 for group 2 ($p < 0.01$). Atrial fibrillation was present in 133 patients (61%): 71 in group 1 (51%) and 62 in group 2 (78%) ($p < 0.01$). Grade 1+ or 2+ mitral regurgitation was present in 59 patients (27%) and a history of thromboembolism in 36 (16%). Severe 3+ aortic regurgitation was present in 13 patients. Two patients had had mitral restenosis after surgical open mitral commissurotomy. In 9 patients, PTMC was performed after resolution of the left atrial cavity thrombus after 3 to 12 months of warfarin treatment. The thrombus resolution was found incidentally in 2 patients⁸ and in the other 7 in an ongoing prospective study of thrombus resolution with warfarin treatment. Chronic obstructive pulmonary lung disease was present in 7, severe kyphoscoliosis in 2, pneumoconiosis

in 1, uremia in 2, systemic lupus erythematosus in 1 and liver cirrhosis in 1 patient.

Percutaneous transvenous mitral commissurotomy

protocol: After diagnostic catheterization and atrial transseptal puncture, baseline hemodynamic measurements were obtained. Cardiac output was measured in triplicate using a 7Fr Swan-Ganz thermodilution catheter. Mitral valve area was calculated by the Gorlin formula. PTMC was performed using Inoue's balloon catheter (Toray Industries, Japan) by the stepwise dilatation technique described previously in detail.² After introduction of the balloon catheter into the left atrium, the distal half of the balloon was slightly inflated with carbon dioxide or diluted contrast medium and a spring wire stylet was inserted into the catheter. The balloon was then manipulated to flow across the stenotic mitral valve and into the left ventricle. The balloon inflation procedure is shown in Figure 2. After the dilatation, left atrial pressure was measured with the balloon catheter and left ventricular pressure with a 7Fr pigtail catheter to assess the mitral valve gradient. Usually, repeat inflations with larger balloon diameters were performed until satisfactory hemodynamic results were obtained or until significant mitral regurgitation developed. All hemodynamic measurements were repeated before the balloon catheter was removed from the left atrium. After withdrawal of the catheter, a right heart oximetry series was repeated.

Intravenous heparin, 100 U/kg body weight, was given immediately after transseptal puncture. After the first 70 cases, the policy of routine 6-week warfarin

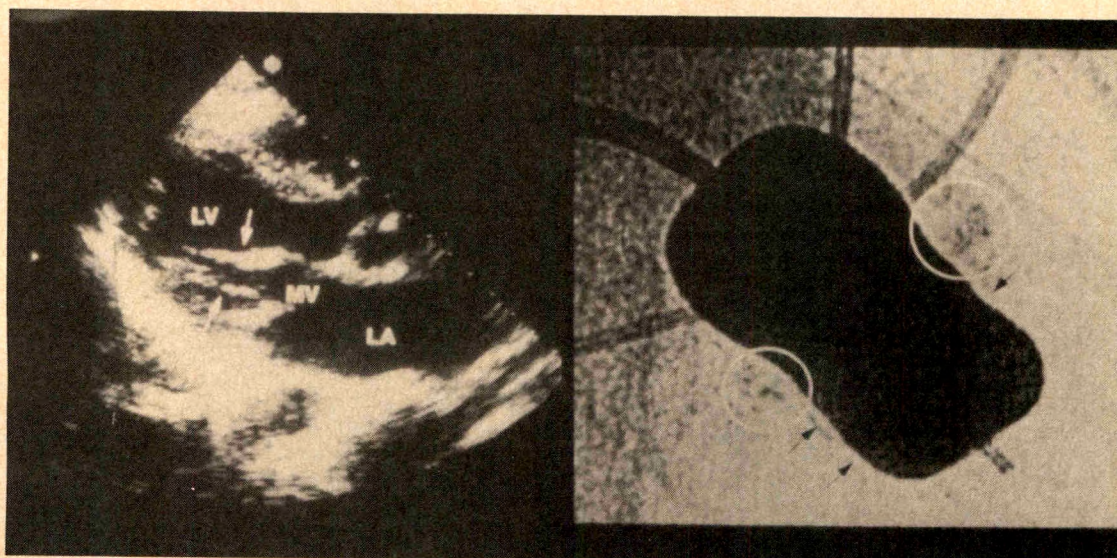


FIGURE 1. *Left*, a long-axis view from 2-dimensional echocardiogram showing severe mitral subvalvular lesions. The chordae tendineae (white arrows) are shortened and severely thickened. *Right*, an angiographic view showing unusual contour of the distal half of the balloon during inflation. Its upper and lower walls are flattened (black arrows) due to compression from the severe subvalvular lesions. The valve is also calcified (white circles). LA = left atrium; LV = left ventricle; MV = mitral valve.

therapy before PTMC in patients with atrial fibrillation was repealed. Patients with a history of embolism were given warfarin for at least 6 weeks before the procedure. PTMC was performed without a surgical team on standby.

Balloon sizing: In the first 59 patients with pliable, noncalcified valves who did not develop significant mitral regurgitation after PTMC, the final balloon size used was then retrospectively correlated with the patient's height, body weight and body surface area. Since height was best correlated with the final balloon size, an empirical balloon reference size (in mm) was derived using the following formula: height (in cm) is rounded to the nearest zero, divided by 10, and 10 is added to the ratio; e.g., if height = 157 cm, then the reference size = $160/10 + 10 = 26$ mm. The initial balloon size was reference size <2 mm in group 1, and reference size <4 mm in group 2. In subsequent dilations, the balloon size was incremented by 1 mm. The final balloon sizes in group 1 ranged from -2 to $+3$ mm from the par reference size and in group 2 from -3 to $+2$ mm.

Echocardiographic studies and treadmill exercise test: Two-dimensional Doppler echocardiography was performed using a Hewlett-Packard phased-array sys-

tem before and 1 day after PTMC. Echocardiographic scores were obtained using the system proposed by Wilkins et al.⁶ Leaflet rigidity, leaflet thickening, leaflet calcification and subvalvular thickening were each scored from 0 to 4 and tallied to a possible maximum of 16. A symptom-limited treadmill exercise test using Naughton's protocol⁹ was performed before and 3 months after PTMC.

Statistical analysis: Continuous variables are expressed as mean \pm standard deviation and were analyzed using Student's *t* test for paired data. Chi-square analyses were used to compare categorical variables. Uni- and multivariate analyses were performed to determine the predictive factors for an increase in mitral regurgitation and for hemodynamically suboptimal results, which were arbitrarily defined as a gain in the valvular area of $<50\%$. The variables analyzed were age, gender, cardiac rhythm, cardiothoracic ratio on chest x-ray, left atrial diameter on M-mode echocardiograms, presence or absence of mitral valve calcification and of severe mitral subvalvular lesions, preexisting mitral regurgitation, balloon size and baseline hemodynamic parameters. The latter category included mitral valve area, mitral valve gradient, mean left atrial pressure, mean pulmonary artery pressure and cardiac out-

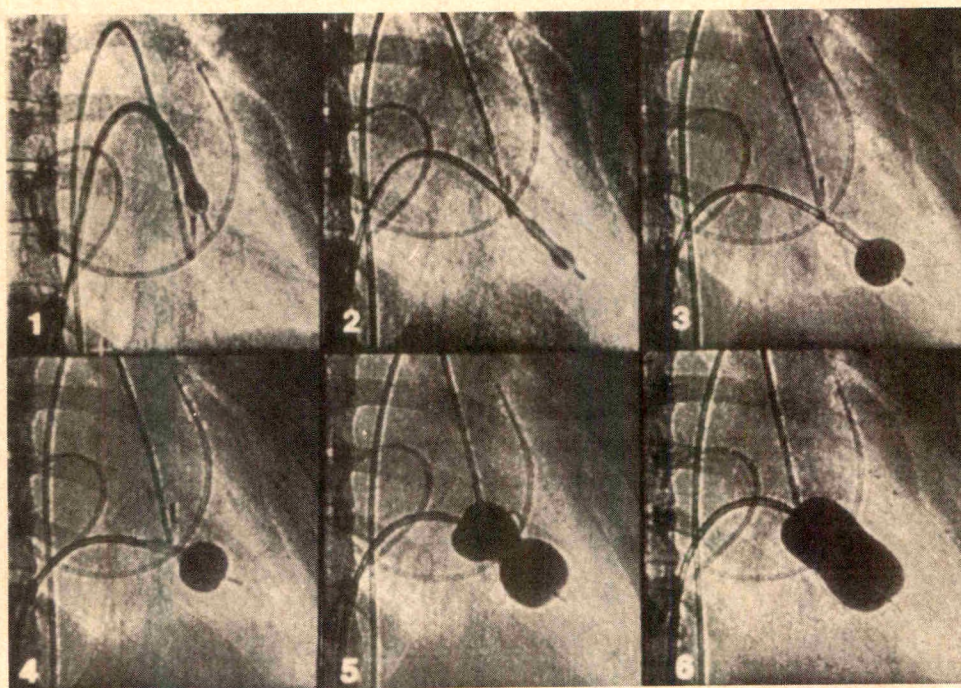


FIGURE 2. Sequence of mitral valve dilatation using Inoue's size-adjustable, self-positioning balloon catheter in angiographic right anterior oblique views: 1 = catheter balloon is in the left atrium; the more compliant distal half of the balloon is slightly inflated with diluted contrast medium. 2 = the balloon is floated across the mitral valve into the left ventricle. 3 = the distal half is further inflated. 4 = the catheter is then pulled back to anchor the balloon at the mitral valve. 5 = as the proximal balloon is inflated, a waist is created by the stenosed valve. 6 = at full inflation, the waist disappears as the commissures are split. The pig-tail catheter in the left ventricle and a Swan-Ganz balloon catheter in the pulmonary artery are also seen in all frames.

TABLE I Failure And Complication Rates (219 Patients)

	No. of Pts.	%
Failures	3	1.4
Complications		
In-hospital mortality	1	0.5
Mitral regurgitation		
Increased	72	33
Severe (grade 3)	12	6
Cardiac tamponade	0	0
Emergency surgery	0	0
Thromboembolism	3	1.4
Atrial septal defect	33	15
Vascular	0	0

TABLE II Hemodynamic Data Before and After Percutaneous Transvenous Mitral Commissurotomy

	All Pts. (n = 204)	Group 1 (n = 130)	Group 2 (n = 74)	p Value
MV area (cm ²)				
Before	1.0 ± 0.3	1.0 ± 0.4	1.0 ± 0.3	NS
After	2.0 ± 0.7*	2.1 ± 0.8*	1.8 ± 0.5*	0.0062
MV gradient (mm Hg)				
Before	13.0 ± 5.1	13.9 ± 5.0	13.2 ± 5.2	NS
After	5.7 ± 2.6*	5.3 ± 2.5*	6.3 ± 2.8*	0.0097
LA (mm Hg)				
Before	24.2 ± 5.6	23.7 ± 5.7	25.1 ± 5.4	NS
After	15.1 ± 5.1*	14.2 ± 4.9*	16.8 ± 5.0*	0.0005
PA (mm Hg)				
Before	39.7 ± 13.0	38.0 ± 12.0	42.5 ± 14.3	0.0185
After	30.6 ± 10.9*	28.4 ± 10.2*	34.6 ± 10.9*	0.0001
CO (liters/min)				
Before	4.4 ± 1.4	4.4 ± 1.1	4.5 ± 1.9	NS
After	4.7 ± 1.2†	4.8 ± 1.1*	4.7 ± 1.3	NS

* p = 0.0001; † p < 0.01 for in-group comparison.

Results of 12 patients who developed 3+ mitral regurgitation after PTMC are excluded.

Group 1 = patients with pliable, non-calcified mitral valves; Group 2 = patients with calcified mitral valves and/or severe mitral subvalvular lesions; CO = cardiac output; LA = left atrium; MV = mitral valve; NS = not significant; PA = pulmonary artery.

TABLE III Predictors For Outcomes of Percutaneous Transvenous Mitral Commissurotomy

Variables	Outcomes		p Value
	Good (n = 167)	Suboptimal* (n = 37)	
Clinical			
Age (years)	40 ± 11	49 ± 11	0.0001
Female (%)	73.1	67.6	NS
Atrial fibrillation (%)	54.8	83.8	0.0012
Left atrial size (mm)	49.8 ± 9.5	55.3 ± 10.1	0.0033
Cardiothoracic ratio	0.61 ± 0.08	0.67 ± 0.09	0.0001
Valvular status			
Echo score	6.3 ± 1.4	7.8 ± 1.5	0.0001
Echo score > 8 (%)	19.5	67.6	0.0001
Calcification (%)	15.8	45.9	0.0001
Severe subvalvular lesions (%)	12.8	40.5	0.0001
Hemodynamic (baseline)			
Mitral valve area (cm ²)	1.0 ± 0.3	1.0 ± 0.3	NS
Mitral gradient (mm Hg)	14.0 ± 5.0	12.1 ± 5.3	NS
Mean left atrial pressure (mm Hg)	24.3 ± 5.3	23.8 ± 7.1	NS
Mean pulmonary artery pressure (mm Hg)	39.9 ± 13.3	38.4 ± 11.7	NS
Cardiac output (liters/min)	4.4 ± 1.1	4.5 ± 2.4	NS

* Gain in valve area < 50% after percutaneous transvenous mitral commissurotomy.
NS = not significant.

put. Life-table analyses were performed by the Kaplan-Meier method.¹⁰ A p value < 0.05 was considered significant.

RESULTS

Transseptal catheterization was successful and uncomplicated in all 219 patients. The mitral valve was successfully dilated in 216 patients (99%).

Technical failures and complications (Table I): Three technical failures occurred among the first 15 attempts: 2 because of failure in manipulating the balloon across the valve and the other because of instrument failure of a prototype balloon catheter.³ The only in-hospital mortality occurred in a group 2 premoribund patient in whom last-resort emergency PTMC created 3+ mitral regurgitation of the densely calcified valve. This patient died 3 days later of multiple organ failure.

The systemic embolisms in 3 patients were seen by transient cerebral ischemic attack, diplopia and left hemiparesis. The diplopia resolved in 3 months and the hemiparesis resolved over several months. None of the 9 patients in whom left atrial thrombi disappeared before PTMC had embolic complications. After PTMC, atrial left-to-right shunts developed in 33 patients (15%). The pulmonary to systemic flow ratio was ≤ 1.5 in 25, and between 1.5 and 1.8 in 8 patients. None of the patients had excessive bleeding requiring blood transfusions.

Hemodynamic and echocardiographic results: Excluding the 12 patients with resultant 3+ mitral regurgitation, PTMC resulted in immediate improvements in the hemodynamic measurements of 204 patients (Table II). Left atrial pressure after PTMC remained > 18 mm Hg in 58 patients, including 22 patients with suboptimal results, all of the 12 patients who developed 3+ mitral regurgitation, and 24 patients with good results. In the patients with 3+ mitral regurgitation, the mean left atrial pressure and v waves increased after the procedure. In the patients with good results, the left atrial pressure remained high because of elevation in the left ventricular end-diastolic pressure > 12 mm Hg. Mean mitral valve area measured by echocardiographic planimetry increased from 0.99 ± 0.49 to 1.78 ± 0.65 cm² after PTMC (p = 0.0001).

Predictors for hemodynamic results: Table II also lists the hemodynamic results of 130 group 1 patients with pliable, noncalcified valves, and 74 group 2 patients with calcified valves or severe subvalvular lesions, or both. Although group 1 had better hemodynamic results than group 2, there were no hemodynamic differences before PTMC except for higher mean pulmonary artery pressure in group 2. Univariate analysis showed older age, atrial fibrillation, larger left atrial size and cardiothoracic ratio, echo score >8 , valvular calcification and severe subvalvular lesions as predictors for suboptimal results (Table III). Multivariate analysis showed an echo score >8 , and valvular calcification and severe subvalvular lesions to be independent predictors for suboptimal hemodynamic results.

Mitral regurgitation: Figure 3 shows changes in the degree of mitral regurgitation as assessed by left ventriculograms before and after PTMC. Mitral regurgitation remained unchanged in most of the 141 cases (65%). It decreased in 3 patients, and either appeared or increased in 72 patients (33%). Of these 72, the degree of mitral regurgitation increased by 1+ in 50 patients, by 2+ in 18 and by 3+ in 4. In all, 12 patients (6%) had 3+ mitral regurgitation after PTMC. As stated previously, 1 group 2 patient with 3+ mitral regurgitation died in the hospital. Another group 2 patient underwent mitral valve surgery 1 month later because of worsening symptoms. Tearing of the anterior leaflet and severe subvalvular lesions were found at surgery. The other 10 patients had clinical improvements.

Increases in the degree of mitral regurgitation were more frequent in group 2 than in group 1. The incidence of the increase by any given grade was 38% in group 2 and 31% in group 1 ($p < 0.001$); the increase of $\geq 2+$ was 14% for group 2 and 9% for group 1 ($p < 0.001$). Multivariate analysis identified balloon oversizing (above the par reference size) in group 1, and preexisting mitral regurgitation and male gender in group 2—but not balloon size—as predictors for the increase of $\geq 2+$.

Immediate clinical results: Two hundred fifteen patients (136 in group 1 and 79 in group 2) were discharged from the hospital, usually on the second day, after successful PTMC. At follow-up visits 1 to 2 weeks later, except for 6 group 2 patients, 209 patients (97%) had improvements in symptoms and in New York Heart Association functional class by at least 1 class (Figure 4). Treadmill exercise tests were available for 159 patients to compare exercise duration before and 3 months after PTMC (Figure 5). The duration increased in all patients.

Late outcomes: Follow-up data were obtained in all 215 patients for at least 6 months: 136 group 1 patients for up to 42 months (median 19) and 79 group 2 patients for up to 31 months (median 13). The cumulative cardiovascular event-free rates are shown in Figure 6. The rate for group 1 was 100% for the entire follow-up period; that for group 2 was 92, 91 and 86% at 6, 12 and 18 months, respectively, and it held at 76% at 24 months and beyond. The 6 group 2 patients, who did

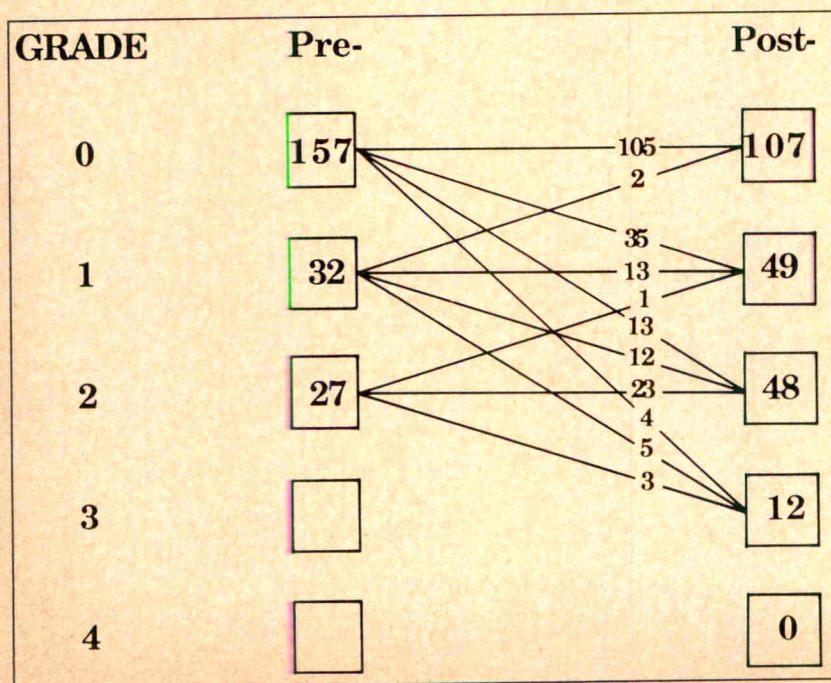
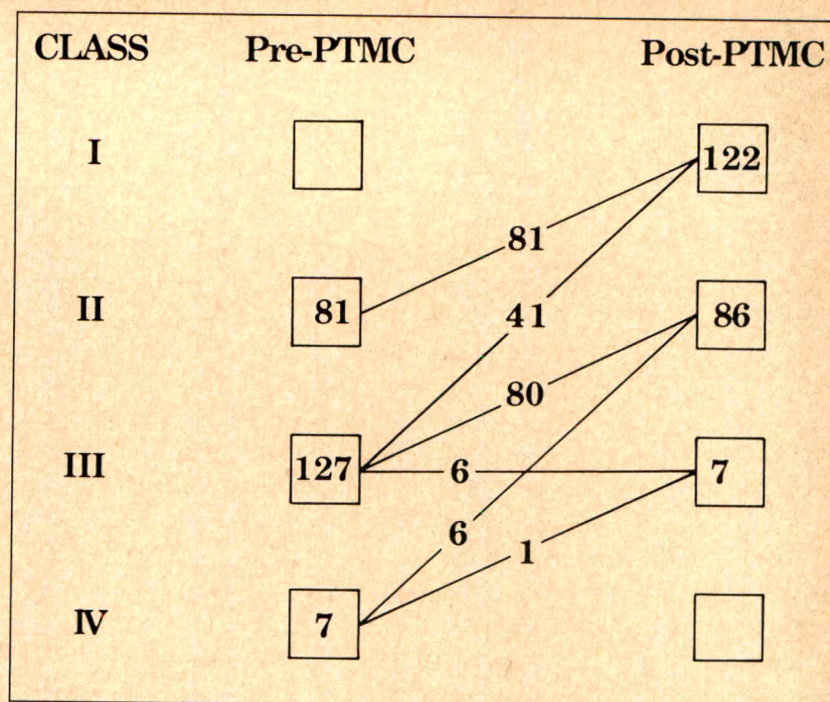


FIGURE 3. Changes in the degree of mitral regurgitation before (Pre-) and after (Post-) percutaneous transvenous mitral commissurotomy (PTMC) in 216 patients, as assessed by left ventriculography according to Sellers et al.⁷

FIGURE 4. Changes in New York Heart Association functional class before and 1 to 2 weeks after percutaneous transvenous mitral commissurotomy (PTMC) in 215 patients.



not improve clinically as previously noted, underwent elective mitral valve replacement within 1 to 22 months: 1 because of severe mitral regurgitation resulting from a tear in the anterior mitral leaflet and the other 5 because of suboptimal hemodynamic results. One group 2 patient developed mitral restenosis in 22 months and underwent mitral valve replacement after repeat PTMC failed to improve the symptoms. Late deaths occurred in 6 group 2 patients: 4 cardiac and 2 noncardiac deaths (traffic accidents). Of the 4 cardiac deaths, 2 were sudden at 7 and 12 months, 1 as a result of multiple cerebral embolisms after 4 months, and the other because of uremia and heart failure 7 months after PTMC. There were continued clinical improvements in the other 67 group 2 patients and all group 1 patients at their last follow-up examinations. None of these patients had clinical evidence of mitral restenosis.

DISCUSSION

This study in a large number of patients in a single center confirms the findings of a previous multicenter trial,² that PTMC using Inoue's balloon-catheter technique indeed increases mitral valve area in patients with severe rheumatic mitral stenosis. The results are also consistent with those of double-balloon mitral valvuloplasty using conventional Mansfield balloon catheters^{11,12} or combinations of a Mansfield and a trefoil balloon catheter.¹¹ As a result of the increase in the valve area, the mitral valve gradient, left atrial pressure and mean pulmonary artery pressure were immediately

reduced. These hemodynamic benefits were mirrored in clinical improvements in the patients' symptoms. In addition, we documented improved exercise tolerance after PTMC by noting increases in treadmill exercise durations.

Complications: Our extensive experience with PTMC yields a high technical success rate (99%) and an encouraging safety record. Only 3 technical failures occurred in our early experience. Transseptal catheterization was successful and uncomplicated in all cases. The only in-hospital mortality occurred in a premoribund patient 3 days after last-resort emergency PTMC created severe mitral regurgitation of the densely calci-

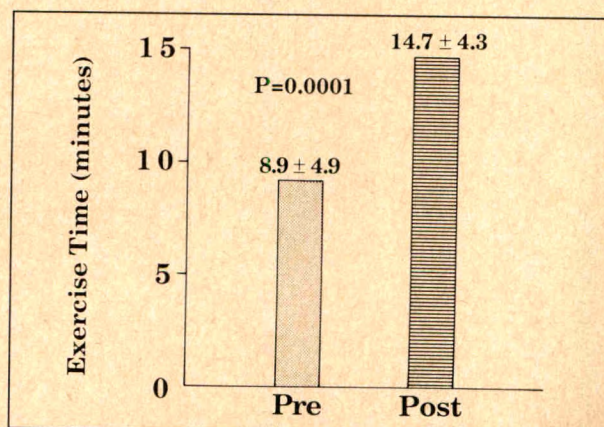


FIGURE 5. Improvements in exercise duration before and 3 months after percutaneous transvenous mitral commissurotomy (PTMC) in 159 patients, as assessed by treadmill exercise test using Naughton's protocol.⁹

fied mitral valve. There was no cardiac tamponade or emergency cardiac surgery.

Systemic embolisms occurred in 3 patients: 2 overly prolonged procedures in our early experience and 1 case of delayed heparin administration after transseptal catheterization. Because the embolisms appeared to be related to inadequate heparinization rather than dislodgement of unsuspected left atrial thrombi, it cannot be overemphasized that intravenous heparin must be given immediately after confirming entry of the transseptal catheter into the left atrium, and should be supplemented if the procedure is prolonged. Embolization has not occurred in any patients with a history of systemic embolism nor in patients in whom PTMC was performed after resolution of left atrial cavity thrombi. New atrial septal defects occurred in 15% of the patients. In these patients, the magnitude of the shunt was small with a pulmonary to systemic flow ratio ≤ 1.8 (mostly ≤ 1.5), and had no hemodynamic or clinical consequences.

Limitations of percutaneous transvenous mitral commissurotomy: Two major drawbacks of PTMC are possible suboptimal hemodynamic results (a gain in the valvular area of $<50\%$) and creation of severe mitral regurgitation. However, our study shows almost all patients with suboptimal hemodynamic results or resultant mitral regurgitation also had clinical improvements. In a small number of these patients who have no improvement, mitral valve surgery can be conducted electively.

As in previous studies,^{2,4,6,11} our findings also show that predictors of suboptimal hemodynamic results of

PTMC are related to the morphology of the diseased mitral valve. Univariate analysis revealed older age, atrial fibrillation, larger left atrial size and cardiothoracic ratio, echo score >8 , valvular calcification and severe subvalvular lesions as predictors for suboptimal results. Multivariate analysis showed an echo score >8 , valvular calcification and severe subvalvular lesions to be independent predictors for hemodynamically suboptimal results.

Mitral regurgitation: The degree of mitral regurgitation increased in one-third of our patients. In most of these patients, the resultant mitral regurgitation was mild to moderate and posed no significant impact on the patients' hemodynamic results or clinical outcomes. In a few of the patients (6%), severe 3+ mitral regurgitation developed. However, in most patients clinical improvements were also observed. None of our patients developed 4+ mitral regurgitation.

Patients with calcified valves or severe subvalvular lesions, or both, are at increased risk of developing mitral regurgitation than those with pliable, noncalcified valves. In the latter patients, increase in mitral regurgitation of $\geq 2+$ is solely related to oversizing the balloon. In the former patients, preexisting mitral regurgitation is a predictor of the increase. In this group, development of significant mitral regurgitation may occur with any balloon size. Therefore, the stepwise dilatation technique should be executed with extra care.

After each dilatation of the valve, its effect and degree of mitral regurgitation should be evaluated by means of pressure measurements, auscultation, color Doppler echocardiography, and, if necessary, left ven-

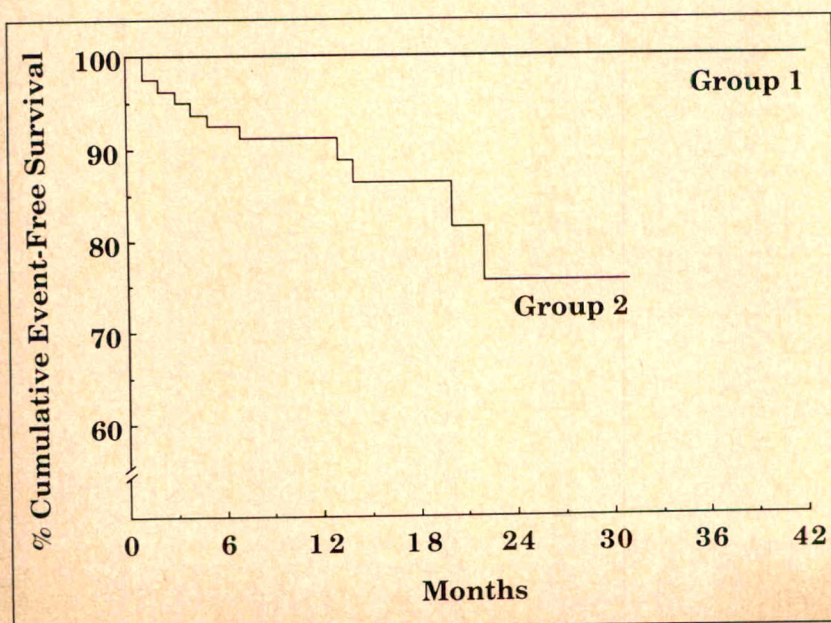


FIGURE 6. Cumulative event-free survival rates for group 1 patients (with pliable, noncalcified mitral valves) and group 2 patients (with calcified valves or severe mitral subvalvular lesions, or both).

triculography. Pressure measurements should include mitral valve gradient derived from measurements of left atrial pressure with the Inoue balloon catheter and left ventricular pressure with the catheter in the left ventricle. Measurement of left atrial pressure alone is insufficient, because suboptimal reduction of the left atrial pressure (e.g., <18 mm Hg) may occur because of (1) inadequate dilatation of the valve, (2) elevation of the left ventricular diastolic pressure despite optimal dilatation of the valve, and (3) development of severe mitral regurgitation. Lack of substantial reduction in mean left atrial pressure along with the development of prominent left atrial *v* waves usually suggests occurrence of severe mitral regurgitation.

Long-term results: Late outcomes of this study are encouraging. Patients with pliable noncalcified valves, usually young and in sinus rhythm, were free of cardiovascular events for as long as 42 months. The long-term effects of PTMC in this group of patients are expected to be excellent. Thus, they are ideal candidates for PTMC. When restenosis of the mitral valve occurs in these patients, it is likely that repeat PTMC can still be performed, as suggested by our experience and reports of successful balloon catheter mitral commissurotomy or valvuloplasty for restenosed mitral valves after surgical commissurotomy.^{2,4,11,12}

In contrast, the late outcomes in patients with calcified valves or severe subvalvular lesions, or both, were less favorable. The event-free survival rate for these patients was 91% at 12 months, and 76% from 24 to up to 31 months. The events included 4 deaths (2 sudden deaths, 1 each from systemic embolism and congestive heart failure), and 7 cases of elective mitral valve surgery. The latter included 5 for suboptimal results, 1 each for severe mitral regurgitation and mitral restenosis. Although the long-term results of PTMC in patients with calcified valves or severe subvalvular lesions, or both, are less favorable, the procedure may yet be a desirable palliative option. PTMC is safe and worthwhile even if clinical improvements are sustained for only several years. When mitral restenosis occurs in these patients, mitral valve surgery can still be performed without difficulties arising from previous thoracotomy.

Patient selection: Our study has demonstrated that PTMC can be performed safely in a variety of patients with mitral stenosis: those with variable valvular status (pliable, calcified or with severe subvalvular lesions), atrial fibrillation, a history of systemic embolism, 1+ or 2+ mitral regurgitation, severe aortic regurgitation, previous surgical commissurotomy, and those at increased surgical risk such as patients with chronic lung

diseases, severe kyphoscoliosis, uremia and liver cirrhosis. The 2 absolute contraindications for PTMC are severe ($\geq 3+$) mitral regurgitation and the presence of a left atrial thrombus.

Selection criteria for PTMC continue to evolve with time and they depend on operator experience, morphologic configurations of the diseased mitral valves and future developments. In the early experience, one should (as we did) adhere to the strict criteria used for surgical closed mitral commissurotomy in selecting only patients with pliable, noncalcified mitral valves for PTMC. With more experience, one can broaden the criteria to include patients with calcified mitral valves or severe mitral subvalvular lesions, or both—namely, patients who would otherwise be likely candidates for mitral valve replacement surgery.

In this study, PTMC was performed without embolic complications in 9 patients whose left atrial cavity thrombi resolved after warfarin therapy, as observed by transthoracic 2-dimensional echocardiography. Whereas presence of small residual left atrial thrombi in the left atrial appendage could not be ruled out without the more sensitive transesophageal echocardiography, we judged it safe to proceed with PTMC.⁸ Although the presence of left atrial thrombus is considered an absolute contraindication for the procedure, this limited experience suggests that it is feasible to first manage patients with mitral stenosis and left atrial thrombus with warfarin treatment if their clinical and hemodynamic status does not warrant immediate surgery. If the thrombus resolves, PTMC can then be performed safely. Further documentation awaits completion of our ongoing prospective study of left atrial thrombus in patients with mitral stenosis receiving warfarin treatment.

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Effects of Aerobic Exercise Training on Symptomatic Women with Mitral Valve Prolapse

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The effects of a 12-week aerobic exercise training protocol on 32 symptomatic women with mitral valve prolapse were studied. Subjects were randomly assigned to control or exercise groups. Exercise subjects completed a 12-week (3 times per week) exercise training program based on guidelines established by the American Heart Association for phase II cardiac rehabilitation programs; control group subjects maintained normal activities. Before and after training, subjects underwent maximal multistage treadmill testing, and measurements were obtained for plasma catecholamine levels at rest and during peak exercise; they completed the State Trait Anxiety Inventory and General Well-Being Schedule. Weekly symptom frequency of chest pain, arm pain, palpitations, shortness of breath, fatigue, headache, mood swings, dizziness and syncope were monitored for the 12-week period. Data were analyzed using multivariate analysis of variance, multivariate analysis of covariance, and analysis of covariance with repeated measures. Compared with control subjects, the exercise group showed a significant ($p < 0.05$) decrease in State Trait Anxiety Inventory scores, an increase in General Well-Being scores, an increase in functional capacity and a decline in the frequency of chest pain, fatigue, dizziness and mood swings. No statistically significant differences were noted in catecholamine levels at rest or during peak exercise. These findings support the use of aerobic exercise in the management of symptomatic women with mitral valve prolapse.

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Although exercise is an accepted adjunct treatment for other forms of cardiac conditions, it has not been studied to any extent for symptomatic mitral valve prolapse (MVP). Recent evidence suggests that autonomic dysfunction, a hyperadrenergic state, metabolic disturbances, or combinations thereof, are a potential explanation for the constellation of symptoms often associated with MVP.¹⁻⁸ Theoretically, the physiologic and psychologic adaptations⁹⁻¹⁸ associated with aerobic exercise should be of benefit in reducing the frequency and severity of the symptoms.

Despite the prevalence of MVP and the voluminous amount of literature on this subject, published studies that address the effects of an aerobic exercise training program on symptomatic persons are not available. Therefore, this study explored the effects of an aerobic training program on the symptoms associated with MVP.

METHODS

Patients: Thirty eight women, aged 21 to 49 years (mean 34), who had been diagnosed with MVP were recruited from private cardiology practices in a large, midwestern city. All subjects had been symptomatic for at least 1 year, and were currently having ≥ 1 symptom on a weekly basis. Auscultatory findings consisted of mobile nonejection systolic click(s) with or without a mid- to late systolic murmur. The diagnosis of MVP was confirmed by M-mode and 2-dimensional echocardiography as previously described.^{19,20} Exclusion criteria were persons with known major pathology, or those with a chronic illness; postmenopausal women; pregnant women; patients for whom medications have had a known effect on cardiac or neuroendocrine function; subjects who were currently exercising on a routine basis (2 to 3 times each week for a minimum of 20 minutes); persons with contraindications to exercise; patients with complex ventricular arrhythmias, significant mitral regurgitation, prolonged QT interval and those with a family history of sudden death due to MVP. Information was obtained through interview and review of medical records.

Study protocol: The study protocol was approved by the Biomedical Sciences Human Subject Review Com-

TABLE I Comparison Between Exercise and Control Groups: Marital and Occupational Status, Race, Age, and Percent of Body Fat

Variable	Exercise (n = 19)	Control (n = 19)
Age (years)	34 ± 6	35 ± 8
Marital status		
Single	3	3
Married	14	14
Divorced	2	2
Occupational status		
Not employed	5	5
Clerical	2	4
Administrative managerial, professional	12	10
Race		
White/black	18/1	17/2
Percent body fat	27 ± 6	24 ± 6

mittee at The Ohio State University. A total of 38 women were randomly assigned to the control or exercise groups; 32 subjects completed the research protocol. Three subjects in each group withdrew for a total attrition rate of 16%. These subjects were unable to complete the protocol because of problems related to child care and work schedules. Pretest measurements in the 6 who withdrew were comparable. Demographic characteristics of the groups are listed in Table I.

SYMPTOM CHECK LIST

Subject # ____ Week # ____ Week ending ____/____/____

Place a number next to the symptom which best indicates the frequency that you experienced this symptom during the past week.

- 5 - All of the time
- 4 - Most of the time
- 3 - A good bit of the time
- 2 - Some of the time
- 1 - A little of the time
- 0 - None of the time

SYMPTOM	FREQUENCY
CHEST PAIN AND/OR CHEST DISCOMFORT	
ARM PAIN AND/OR DISCOMFORT	
PALPITATIONS/SKIPPED BEATS	
SHORTNESS OF BREATH	
FATIGUE	
HEADACHE	
ANXIOUS (FEELING NERVOUS OR FRIGHTENED)	
MOOD SWINGS	
DIZZINESS AND/OR LIGHTHEADEDNESS	
PASSING OUT SPELLS	
OTHER	

FIGURE 1. Weekly symptom check list. (Copyright 1990 K. A. Scordo. Reprinted with permission.)

Pretest and post-test data included estimated maximal oxygen uptake (ml/kg-min) as described previously,²¹ State Trait Anxiety Inventory, General Well-Being Schedule and resting and peak exercise catecholamine levels. At the end of each week, subjects completed a symptom checklist (Figure 1). Five cardiologists who served as the expert panel were asked to list what they recognize as the most frequently occurring symptoms. Based on their responses, as well as items from published reports, the questionnaire was constructed. Because the purpose of this questionnaire was to serve as a measure of the subject's perception of their symptom frequency, and because the patient's subjective measures are often in conflict with objective data, no attempt was made to correlate symptoms with diagnostic testing. For example, it is not unusual for patients to record "palpitations" during 24-hour Holter monitoring while having sinus tachycardia.²

The following pre- and post-test procedures for exercise testing and plasma catecholamines were: Before the start of the graded exercise stress test (standard Bruce protocol), and after a 20-minute rest period in a sitting position, venous blood was drawn from a forearm vein through an indwelling catheter. Post-test plasma levels were obtained at approximately the same time of day as the pretest levels were drawn. Subjects were instructed to avoid drinking coffee and tea and smoking cigarettes for 3 hours before the collection of the sample. A second venous sample was obtained during the exercise stress test at the highest heart rate achieved. Postexercise samples were drawn at this same heart rate. Specimens were kept on ice, centrifuged and kept frozen until the analysis was performed. Norepinephrine and epinephrine levels were determined using [3H] radioenzymatic assay system (Amersham's Cat-a Kit). The State Trait Anxiety Inventory and General Well-Being Schedule were administered using standardized instructions.

Exercise group: Subjects in this group exercised 3 times a week for a total of 12 weeks. The aerobic exercise training program was based on guidelines established by the American Heart Association.²² The format for each exercise session included a warm-up period, a training or endurance phase and a cool-down period. The intensity of the work load was designed to maintain heart rate response between 60 and 85% of maximum and a perceived exertion of "somewhat hard" on the Borg scale of rated perceived exertion. Depending on individual fitness levels, subjects began with a minimum of 10 to 15 minutes of continuous exercise. This was increased by approximately 5 minutes each week until 45 to 60 minutes of continuous aerobic exercise was reached. Subjects exercised using

≥1 of the following equipment: treadmill, Tunturi bicycle ergometer and Schwinn AeroDyne stationary bicycle. Subjects were monitored by the use of a Quinton Paragon 420 telemetric monitoring system. All exercise sessions were held in an outpatient, free-standing cardiac rehabilitation center.

Control group: This group received no exercise treatment. Subjects were instructed to maintain their normal activity level. If a subject began an informal or formal exercise program, they were excluded from the study. The post-test measure of functional capacity served to validate the subject's self report of activity. After completion of the study, these subjects were given the opportunity to participate in the same exercise program as that of the exercise group.

Statistical analysis: Initial analysis demonstrated a substantial relation between pre- and post-test functional capacity ($r = 0.60$, $p < 0.001$) and a moderate association between pretest functional capacity and post-test exercise epinephrine ($r = -0.48$, $p < 0.015$). Moderate inverse relationships ($p < 0.05$) were noted between functional capacity and palpitations ($r = -0.45$), shortness of breath ($r = -0.45$), anxiety ($r = -0.35$) and mood swings ($r = -0.32$). Four analyses were done: (1) multivariate analysis of variance was used to determine treatment effects on State Trait Anxiety Inventory and General Well-Being Schedules; (2) multivariate analysis of covariance (ANCOVA) was used to determine the effect of the exercise training program on catecholamines with functional capacity as the covariate; (3) ANCOVA was used to analyze the effect of the treatment on functional capacity after adjusting for initial level of fitness; and (4) ANCOVA with repeated measures with functional capacity as the covariate was used to determine treatment effects on symptoms. Since there was no variance in the symptom syncope, this symptom was not entered into the analyses. With the exception of those analyses using ANCOVA with repeated measures, pre- to post-test comparisons were done on the difference or gain scores. All analyses except ANCOVA with repeated measures were conducted with the SPSS-X Data Analysis System. ANCOVA with repeated measures was executed with the BMDP Statistical Software. A p value < 0.05 was considered statistically significant. To compensate for pretest/post-test sensitization, an improvement of ≥5% in functional capacity was considered significant.

RESULTS

Symptoms: At pretest, all subjects reported ≥3 symptoms on a weekly basis. The percentage of frequency of each symptom at pretest is depicted in Figure 2. One additional symptom reported by 4 subjects was

a feeling of a lump in the throat. The true incidence of symptoms in patients with MVP syndrome is unknown.²³ The higher percentage of the frequency of symptoms documented in this study may reflect a selection bias.

ANCOVA with repeated measures (1 grouping factor, experimental versus control, and 1 within factor, time) demonstrated a significant difference over time between the 2 groups for the symptoms of chest pain, fatigue, dizziness and mood swings. The lack of statistical significance for the remaining symptoms may be related in part to the small sample size with resulting low power (< 0.45). This is quite conceivable since each subject was analyzed for 9 symptoms over a 12-week period. Except for the symptom headache, a significant pattern or within-group effect was noted for all symptoms.

Most symptoms declined in frequency over time for the exercise group. The greatest decline was seen at week 6. This may have been related to physiologic adaptations seen after several weeks of exercise training. Chest pain, palpitations and dyspnea declined in frequency in both groups. This decline may reflect various physiologic changes such as varying catecholamine levels, total circulating blood volume, or a tendency toward greater acceptance and understanding of symptoms, or a combination of these.

General well-being, state and trait anxiety: The exercise group demonstrated a significant improvement in general well-being and a reduction in state and trait anxiety (Table II). Mean scores for the exercise group represent marginal positive well-being, whereas scores for the control group correspond with mild problem-indicative stress. The lower mean scores for the exercise group on the State Trait Anxiety Inventory correspond with a decrease in anxiety level.

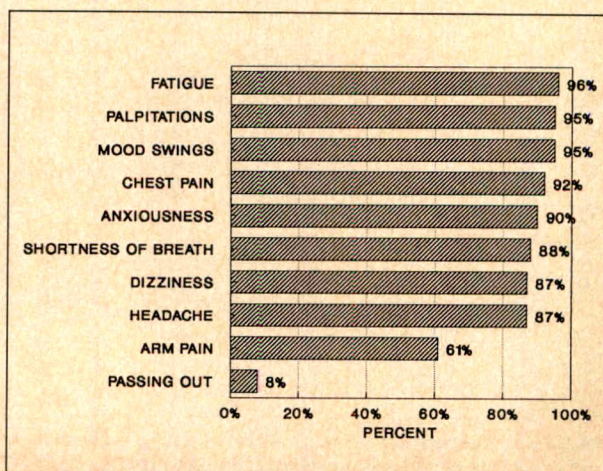


FIGURE 2. Percent of pretest symptom frequency for exercise and control groups combined.

TABLE II Observed Post-Test (Mean \pm Standard Deviation) and Multivariate Analysis of Variance for the Dependent Measures General Well-Being Schedule, State and Trait Anxiety*

Variables	SD	Mean Scores Between Groups	Univariate Analysis F (df, 1,31)	p Value
General Well-Being Schedule		3,319	12	<0.001
Control group	53 \pm 16			
Exercise group	72 \pm 16			
State Anxiety Inventory		4,300	8	<0.006
Control group	44 \pm 11			
Exercise group	33 \pm 12			
Trait Anxiety Inventory		4,317	6	<0.017
Control group	48 \pm 11			
Exercise group	37 \pm 12			

* Wilks' λ 0.64, F = 6; df = 3,30; p < 0.004.
df = degrees of freedom; SD = standard deviation.

Functional capacity: The estimated maximal oxygen uptake at pretest, as compared with established norms,²⁴ revealed a low functional capacity in 4 subjects (11%), fair in 10 subjects (26%), average in 15 subjects (39%) and good in 9 subjects (24%). Resting heart rates ranged between 60 to 106 beats/min (mean 79). Supine resting systolic blood pressure ranged from 82 to 142 mm Hg and diastolic from 54 to 90 mm Hg (mean 107/68 mm Hg). Time on the multistage treadmill test ranged from 4 to 11 minutes.

No significant arrhythmias, or ST-segment and T-wave abnormalities were noted during graded treadmill exercise testing or during the exercise sessions. There were no complaints of an increase in symptoms for any of the subjects in the exercise group.

Pearson's correlation coefficient failed to demonstrate a significant relation between age and functional

capacity. This is of interest, particularly because of the relatively young ages of the subjects. In general, based on normal healthy populations, there is an inverse relation between age and functional capacity.²⁵ There was a significant increase in functional capacity for the exercise group (Figure 3); no significant changes were noted in the control group (Figure 4). The observed means \pm standard deviation for functional capacity were 30 \pm 8 (ml/kg-min) for the control group and 41 \pm 6 (ml/kg-min) for the exercise group (p < 0.001).

Plasma catecholamines: At pretest, 47% of the subjects had elevated resting norepinephrine levels (9 subjects in each group) and 18% had elevated resting epinephrine levels (3 subjects in the control and 4 in the exercise groups). Because of technical difficulties, only 20 specimens were analyzed (9 in the exercise and 11 in the control groups); the resulting power was <0.45. Although there was a decline in resting epinephrine and exercise epinephrine, this was not statistically significant (see Table III). The higher levels of exercise norepinephrine for the exercise group are most likely related to the higher work loads achieved after training.

DISCUSSION

The findings of this study suggest that aerobic training has potential as an intervention to improve psychologic well-being and reduce the frequency of symptoms associated with MVP.

A common clinical finding associated with MVP is the reported variation in symptoms over time. From descriptive data obtained from the comments written by subjects on the weekly symptoms check list, it was noted that the greatest increase in symptoms occurred during menses, with excessive fatigue, or during emotional stress related to employment or family life, or both.

At the completion of their participation, subjects in the exercise group commented that situations or stress-

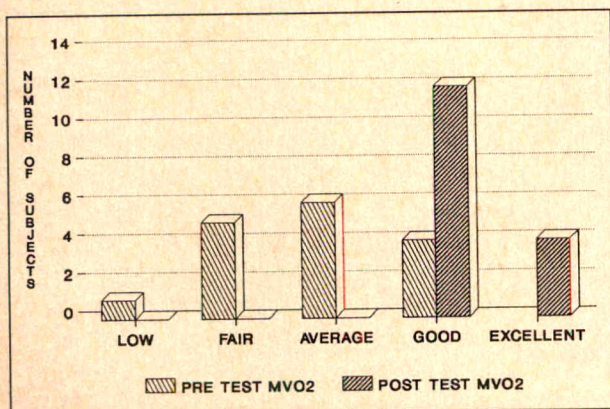


FIGURE 3. Comparison of the exercise group pretest-post-test estimated maximal oxygen consumption (MVO₂) (ml/kg-min).

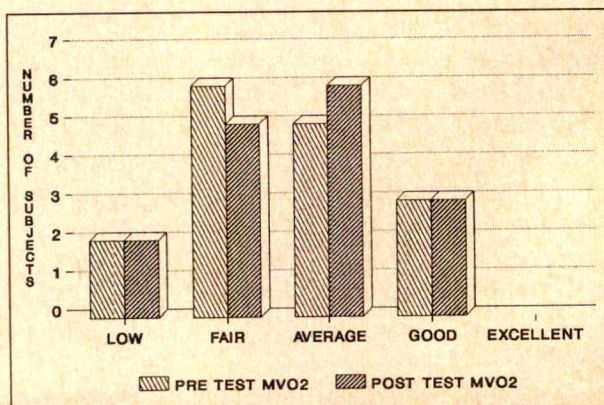


FIGURE 4. Comparison of the control group pretest-post-test estimated maximal oxygen consumption (MVO₂) (ml/kg-min).

ors that usually produced their symptoms either did not produce these symptoms, or the symptoms were less intense. A modified stress response became most evident for 2 of the exercise group subjects, who, before participating in the research protocol, presented themselves on a weekly to bimonthly basis to the emergency room because of chest pains or palpitations, or both. These persons related how fearful they were of their symptoms; they had a feeling of impending death. These same persons reported that they had not been to an emergency room since participating in the research study. Conceivably, exercise may reduce the utilization of emergency room visits. However, more data are needed to substantiate this potential outcome.

Most subjects stated that they felt "generally miserable and wiped out" within 24 hours after the maximal graded exercise stress test. Subjects complained of nausea or noted an increase in their present symptoms. This was evident at pretest for both groups, but less evident after post-testing for the exercise group. This is consistent with clinical complaints of increased symptoms after intense unaccustomed exertion. This is an issue that warrants further investigation.

An anecdotal finding was reports of changes in sleeping patterns. Subjects who had difficulty sleeping noted that they could sleep better; those who believed they slept for long periods of time and remained fatigued during the day, slept less and felt more energetic. This issue should be addressed in further studies.

Study limitations: There are several limitations regarding the results of this study. Because of the small sample size and problems associated with the use of multiple statistical tests on such a sample, the results need to be interpreted with caution. Results from this study are restricted to female patients with MVP who are on a specific aerobic exercise protocol. These results should not be generalized to other groups of patients with MVP, such as men, or those with significant dysrhythmias. It cannot be assumed that other exercise techniques would generate the same results. Familiarization with the treadmill during the exercise training period may have positively influenced the results of the graded exercise stress test. Also, psychologic or social influences of being in a support group during exercise could have served as an unanticipated intervention.

Acknowledgment: The author gratefully acknowledges the criticism and advice of Mary MacVicar, RN, PhD, the support of Fuheid S. Daoud, MD, and the assistance of Linda Hoffsis, MA, Michael Frank, MEd, Nancy Homan, RN, and the staff at the Health Promotion and Rehabilitation Center, Cincinnati, Ohio.

TABLE III Observed Post-Test (Mean \pm Standard Deviation) and Multivariate Analysis of Covariance for the Dependent Measures of Resting and Exercise Norepinephrine and Epinephrine*

Variables	SD	Mean Scores Between Groups	Univariate Analysis F (df 1,17)	p Value
Resting epinephrine		713	3	<0.10
Control group	40 \pm 23 [†]			
Exercise group	26 \pm 12			
Resting norepinephrine		13	0.003	<0.96
Control group	331 \pm 63 [†]			
Exercise group	330 \pm 70			
Exercise epinephrine		1,121	0.04	<0.84
Control group	164 \pm 236 [†]			
Exercise group	127 \pm 95			
Exercise norepinephrine		969,875	2	<0.20
Control group	1,091 \pm 574 [†]			
Exercise group	1,564 \pm 883			

* Wilks' λ 0.64, F = 1.96, df 4,14, p < 0.16, power < 0.45.

[†] ng/liter.

df = degrees of freedom; SD = standard deviation.

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Validity of an Early Postoperative Baseline Doppler Recording After Aortic Valve Replacement

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In 131 patients undergoing aortic valve replacement (53 bioprostheses, 78 mechanical), the pressure decrease across the prosthesis was recorded with Doppler ultrasound at a baseline study early postoperatively (mean 11 ± 5 days) and compared with a repeat measurement 3 to 5 months later. At baseline the hemodynamic state was markedly different, with increased heart rate (89 ± 14 vs 74 ± 13 beats/min, $p < 0.001$) and decreased left ventricular ejection time index (367 ± 21 vs 390 ± 22 , $p < 0.001$). A minor and clinically insignificant decrease in pressure decrease with time was found. The 95% confidence interval for the difference was 0.2 to 3.0 and 0.2 to 1.7 mm Hg for the peak and the mean pressure decrease, respectively. The change in pressure decrease was statistically significant for bioprostheses (mean 16 ± 5 vs 14 ± 4 mm Hg, $p < 0.01$) and smaller (≤ 23 mm) valves (mean 17 ± 4 vs 15 ± 4 mm Hg, $p < 0.01$), whereas no significant changes were found for mechanical valves or valves of a larger size. The change in mean pressure decrease from baseline to the second examination was within ± 5 mm Hg for 82% of patients. It is concluded that despite a different hemodynamic state in the early postoperative period, the pressure decrease across aortic valve prostheses obtained at this time can be used as a reference for later comparison.

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Doppler ultrasound has been established as a valuable tool in the evaluation of aortic valve prostheses.¹⁻³ The noninvasively obtained pressure decrease has been shown to correlate well with invasive recordings,^{1,2,4} and several reports give reference values for velocities and pressure decreases across different types of prosthetic aortic valves.⁵⁻⁷ There is considerable overlap among different types and sizes of prostheses.⁸⁻¹⁰ The pressure decrease across normally functioning prostheses will, in addition to the characteristics of the prosthesis, be influenced by several patient-related factors (heart rate, stroke volume, myocardial function). Therefore, a baseline recording for comparison could be useful in the assessment of prosthetic valve function at follow-up. This could be performed early postoperatively, but the result at this time might be influenced by an altered hemodynamic state (heart rate, loading conditions, pericardial effusion) as well as a more limited access in some patients. The aim of our study was to assess the validity of the pressure decrease obtained across aortic valve prostheses in the early postoperative period as a reference for later comparison.

METHODS

Patients: Patients undergoing aortic valve replacement from 1983 to 1989 were consecutively included in the study when a Doppler ultrasound study with technically adequate recordings could be performed before hospital discharge and a second study 3 to 5 months postoperatively. Patients with more than minor aortic regurgitation at the baseline study were not included and patients who later developed signs of prosthesis malfunction were excluded. Mean time from surgery to the first examination was 11 ± 5 days. A total of 131 patients were included, 53 with a *bioprosthesis* (24 Carpentier Edwards, 28 Carpentier Edwards supraannular, 1 Xenotech), and 78 with a *mechanical valve* (60 Medtronic-Hall, 13 Duromedics, 5 Sorin). A subgroup of 71 patients underwent a third examination 12 to 18 months postoperatively. The Doppler recordings were performed with an Irex III B, Irex Meridian or VingMed CFM 700 with a 2.0- or 2.5-MHz transduc-

TABLE I Pressure Decrease (mm Hg), Heart Rate and Left Ventricular Ejection Time Index at Baseline and at Three to Five Months Postoperatively (n = 131)

	Baseline	3 to 5 Months	95% CI
Peak	27 ± 9 (10–64)	26 ± 8 (12–58)	0.2–3.0
Mean	15 ± 5 (5–34)	14 ± 4 (6–26)	0.2–1.7
HR (beats/min)	89 ± 14 (54–120)	74 ± 13 (45–111)	12–17
LVETI	367 ± 21 (312–429)	390 ± 22 (342–456)	–19 – –27

Ranges are given in parentheses.
HR = heart rate; LVETI = left ventricular ejection time index; Mean = mean pressure drop; Peak = peak pressure drop; 95% CI = 95% confidence interval for the difference.

TABLE II Change in Pressure Decrease (mm Hg) from Baseline to Recording at Three to Five Months According to Prosthesis Type and Size

Type and Size	Baseline	3 to 5 Months	95% CI
Bioprostheses (n = 53)			
Peak	28 ± 10 (11–64)	24 ± 7 (13–41)	0.7–5.7
Mean	16 ± 5 (6–34)	14 ± 4 (7–23)	0.6–3.4
Mechanical (n = 78)			
Peak	27 ± 9 (10–48)	27 ± 9 (12–58)	–1.1–2.1
Mean	14 ± 5 (5–30)	14 ± 5 (6–26)	–0.7–1.1
Size 20 to 23 mm (n = 53)			
Peak	31 ± 8 (16–47)	29 ± 8 (18–58)	0.6–4.9
Mean	17 ± 4 (5–30)	15 ± 4 (6–26)	0.4–2.7
Size 25 to 31 mm (n = 78)			
Peak	24 ± 9 (10–64)	24 ± 8 (12–47)	–1.2–2.7
Mean	14 ± 5 (5–34)	13 ± 4 (6–23)	–0.5–1.6

Abbreviations as in Table I.

er. The transprosthetic velocities were recorded by continuous-wave Doppler. A computerized digitizer was used for envelope tracing of the velocity curves and calculation of peak and mean pressure decreases. In patients with sinus rhythm, ≥ 3 consecutive beats were averaged; in patients with atrial fibrillation, ≥ 5 consecutive beats were averaged. Left ventricular outflow tract velocities were recorded using pulsed-wave Doppler, with the sample volume positioned just below the prosthesis. The net gradient (corrected for subvalvular velocities) was obtained by subtracting the left ventricular outflow tract velocities (Vlvot) in the Bernoulli equation: net gradient = $4(V_{\max}^2 - V_{\text{lvot}}^2)$.^{5,11} In the first part of the study period, the subvalvular recordings were not routinely documented by strip-chart recording in cases where the subvalvular velocity did not exceed 1 m/s. Recordings for calculating the net transprosthetic pressure decrease at both examinations were

available in 41 patients. Left ventricular ejection time was measured from the start of the opening to the start of the closing signal of the prosthesis. Paper speed was 50 to 75 mm/s. Left ventricular ejection time index was calculated according to the formula of Weissler.¹²

Reproducibility: In a recent study from our laboratory, interobserver variability in recordings of peak velocities across aortic valve prostheses was assessed (Rossvoll, unpublished data). With independent analysis of the same recordings, the coefficient of variation was 4%; with both recording and analysis done independently, the coefficient of variation was 7%.

Statistical analysis: All values are expressed as mean \pm standard deviation. Paired data were compared using a 2-tailed paired *t* test. The 95% confidence interval for a difference is presented, and when this did not include 0, statistical significance was considered. Linear regression analysis was used comparing the change in uncorrected (total) with the change in corrected (net) gradients between the 2 examinations.

RESULTS

Table I summarizes the data at baseline compared with the findings 3 to 5 months later. A minor but statistically significant decrease in both the peak and the mean pressure decrease was found. There was a marked decrease in heart rate and an increase in left ventricular ejection time index between the examinations. In patients with bioprostheses, a statistically significant decrease in pressure decrease was found, in contrast to the group with mechanical valves (Table II). Table II also lists the pressure decrease related to prosthesis size. In small valves (≤ 23 mm) there was a statistically significant decrease in pressure decrease not found in larger prostheses.

Figure 1 shows the individual variation in pressure decrease. The change in mean pressure decrease from baseline to the examination 3 to 5 months later was within ± 5 mm Hg in 107 patients (82%). In only 4 patients (3%) did the change in mean pressure decrease exceed ± 10 mm Hg. Among the 24 patients with a change in mean pressure decrease $> \pm 5$ mm Hg, the direction of the change in 17 was toward a lower pressure decrease. Only 7 patients (5%) showed an increase of > 5 mm Hg in mean pressure decrease. The changes in peak pressure decrease were highly correlated to the changes in mean pressure decrease ($r = 0.96$). In absolute values, however, the changes in peak pressure decrease were greater (Figure 1).

Between 3 to 5 and 12 to 18 months, there was a further decrease in heart rate and an increase in left ventricular ejection time index (Table III). Pressure decrease also tended toward a further decrease; however, the change was not statistically significant for the mean

pressure decrease. Figure 2 shows a close correlation between the changes in total gradients and the changes in gradients corrected for subvalvular velocities between the 2 examinations.

Pathologic obstructions: In 2 patients with thrombotic obstruction of a mechanical valve confirmed by surgery or autopsy, the mean gradient exceeded the mean value for normally functioning valves by >6 standard deviations and the increase from baseline for each was 31 and 56 mm Hg. In 2 patients who underwent reoperation for a stenotic bioprosthesis, a mean gradient of 68 and 78 mm Hg was recorded for each.

DISCUSSION

Hemodynamic state: The markedly different hemodynamic state at baseline is demonstrated by the increased heart rate and the decreased left ventricular ejection time index. A shortening of the left ventricular ejection time early after aortic valve replacement is mainly thought to be caused by a more rapid rate of shortening of the ventricular muscle as the afterload is substantially reduced, especially in the case of aortic stenosis.¹³⁻¹⁵

Theoretically, the altered hemodynamic state early postoperatively could be by different mechanisms influence the pressure decrease across aortic valve prostheses in either direction. With increase in heart rate, diastolic filling and stroke volume will decrease, resulting in a

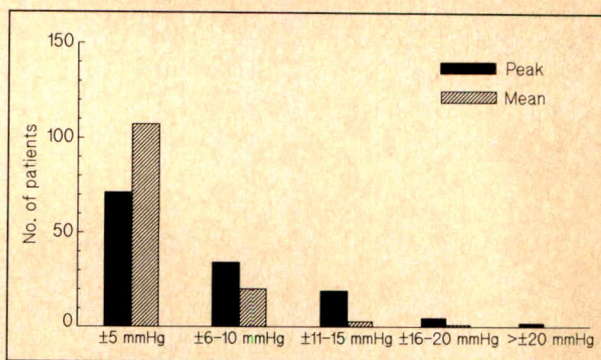


FIGURE 1. Individual variation in the peak and the mean pressure decrease from baseline to the second recording.

reduced pressure decrease. However, for the same stroke volume, a decreased ejection time would result in an increased mean pressure decrease. These considerations are in accordance with the results of Thormann et al,¹⁶ where patients with aortic valve prostheses were examined at different hemodynamic states induced experimentally. During pacing at increasing heart rates, the gradient across the prostheses decreased. During isoproterenol infusion, stroke volume increased and systolic ejection period per beat decreased, with a considerable increase in gradient.

Individual variation: For the group as a whole, the differences in pressure decreases from baseline to the recording at 3 to 5 months were small, with narrow confidence intervals, and considered to be without clinical

TABLE III Baseline Data Compared with Repeat Measurements at Three to Five and 12 to 18 Months (n = 71)

	Baseline	95% CI	3 to 5 Months	95% CI	12 to 18 Months
Peak (mm Hg)	27 ± 8	-0.2-3.2	25 ± 8	0.1-2.8	24 ± 7
Mean (mm Hg)	15 ± 5	0-2.0	14 ± 5	-0.1-1.4	13 ± 4
HR (beats/min)	89 ± 14	11-17	75 ± 13	2-7	71 ± 12
LVETI	369 ± 20	-16--27	391 ± 22	-10--18	404 ± 19

Abbreviations as in Table I.

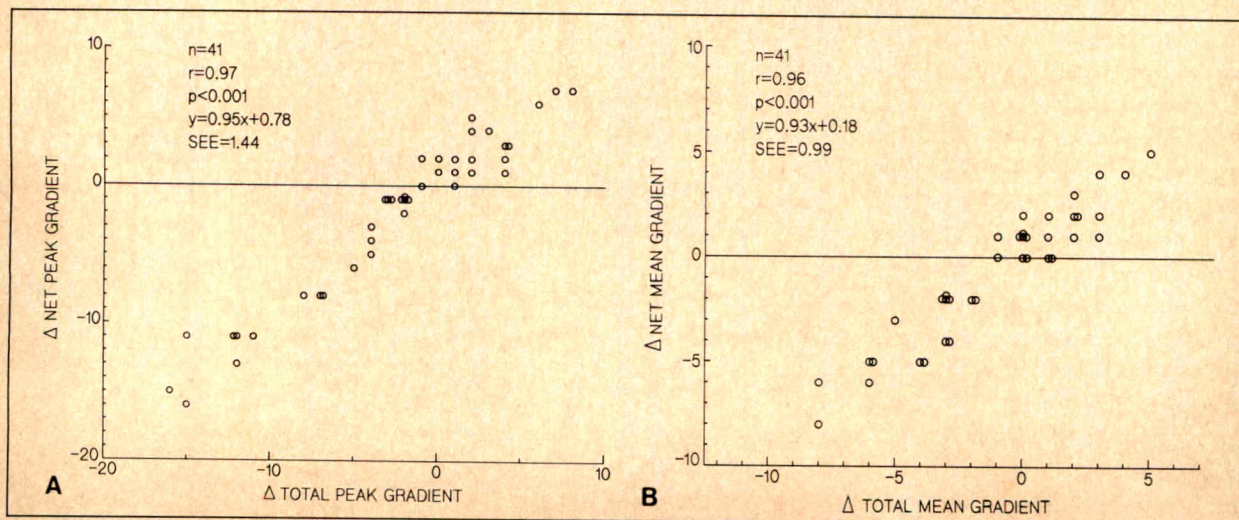


FIGURE 2. Changes in total peak (A) and total mean (B) pressure decrease versus changes in net (corrected for prevalvular velocities) pressure decrease from baseline to the second examination.

cal significance (Table I). The individual variation in mean pressure decrease was within ± 5 mm Hg in 82% of the patients (Figure 1), indicating that the pressure decrease obtained at a hemodynamically more stable state shows no or only minor deviation from baseline in the majority of cases. Among patients where the mean pressure decrease differed by $>\pm 5$ mm Hg from baseline, the direction of change was mostly toward lower gradients with time. This suggests that in patients with normally functioning aortic valve prostheses, a significant increase in pressure decrease from baseline is rather uncommon. The largest increase in mean pressure decrease was from 10 to 22 mm Hg in a patient with atrial fibrillation and a ventricular rate of 101 beats/min at baseline, and sinus rhythm with a heart rate of 48 beats/min at the second examination. This illustrates that the pressure decrease across normally functioning aortic valve prostheses may occasionally vary considerably when the hemodynamic state is markedly changed. In the presence of a significant increase in pressure decrease, a careful search for valvular and paravalvular leaks as well as an accurate assessment of left ventricular outflow tract velocities is mandatory. If the increased pressure decrease cannot be explained by changes in stroke volume due to a slower heart rate or significant leaks, an abnormal obstruction of the prosthesis should be suspected.

Valve type and size: The pressure decrease obtained at baseline was more representative for later findings in mechanical valves than for bioprostheses and in larger than smaller prostheses (Table II). The difference found according to valve size could be explained by a smaller orifice area causing more change in pressure decrease with changes in flow. The difference noted according to valve type could indicate that in bioprostheses a slight decrease in resistance to flow may occur during the first months after implantation. These findings are in accordance with an in vitro durability study of bioprosthetic valves performed by Schuster and Wagner.¹⁷ They reported a decrease in the transprosthetic peak velocity with time due to an increase in flow area.

Corrected versus uncorrected gradients: As the pressure decrease obtained by continuous-wave Doppler is influenced by preavalvular velocities, the obstruction is most correctly assessed by the net gradient across the prosthesis.¹¹ However, the very close correlation in differences between the uncorrected and corrected gradients (Figure 2) suggests that in the follow-up of patients, the changes found in gradient will be similar whether the total (uncorrected) or the net (corrected) gradient is used, as long as the changes are due to changes in flow. In the presence of abnormal obstruction,

however, this relation is likely to change, and the ratio of the subvalvular to the valvular velocities may prove to be an even more useful parameter in the follow-up of patients with aortic valve prostheses.³ In clinical practice, therefore, we would recommend that subvalvular velocities always be recorded.

Clinical implications: Although the hemodynamic state is markedly different from early after aortic valve replacement to follow-up, the pressure decrease obtained across aortic valve prostheses at an early postoperative recording is representative as a reference for later comparison. A practical recommendation based on our findings is that patients undergoing aortic valve replacement should routinely be examined by Doppler ultrasound before hospital discharge.

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Ventricular Late Potentials and Induced Ventricular Arrhythmias After Surgical Repair of Tetralogy of Fallot

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Ventricular tachycardia (VT) and sudden death are rare but recognized complications after surgical repair of tetralogy of Fallot. We prospectively studied 31 patients (19 boys and 12 girls, mean age \pm standard deviation 7 ± 4 years) with postoperative tetralogy of Fallot, by means of right-sided cardiac catheterization, 24-hour Holter monitoring, body-surface and intracavitary signal-averaging (gain 10^5 to 10^6 , filters of 100 and 300 Hz) and programmed ventricular stimulation (1 and 2 extrastimuli, 3 basic cycle lengths, right ventricular apex and outflow tract). All patients were asymptomatic and none had documented or suspected ventricular arrhythmias. Ventricular late potentials were detected in 10 of 31 patients (32%) and spontaneous ventricular arrhythmias in 12 of 31 patients (39%). No sustained VT was induced by programmed ventricular stimulation but nonsustained VT was induced in 3 patients (10%). Patients with inducible VT more often had late potentials (3 of 3 vs 7 of 28, $p < 0.01$), and spontaneous ventricular premature complexes (VPCs) during Holter monitoring (3 of 3 vs 9 of 28, $p < 0.05$). To predict VT inducibility, late potentials had a sensitivity of 100%, a specificity of 75%, a positive predictive value of 30% and a negative predictive value of 100%. For spontaneous VPCs, the figures were 100, 68, 25 and 100%, respectively. It is concluded that shortly after repair of tetralogy of Fallot, the presence of both spontaneous VPCs and ventricular late potentials are associated with an increased incidence of inducible VT. Conversely, the absence

of VPCs and ventricular late potentials may identify patients at low risk of subsequent ventricular arrhythmias.

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Late sudden death is a rare but recognized complication after surgical repair of tetralogy of Fallot.¹⁻⁵ The causes of death are either advanced conduction disturbances^{1,3,6} or ventricular arrhythmias.^{1,7-10} Electrocardiography at rest,^{7,11} exercise testing^{4,12,13} and Holter monitoring^{12,14,15} have been recommended to identify patients at risk of sudden death, but the true prognostic value of these tests is uncertain.¹⁶ Fractionated electrograms at multiple sites in the right ventricle¹⁷ and body surface or intracavitary late potentials,¹⁸ or both, have been described recently in postoperative tetralogy of Fallot; these abnormalities may represent delayed activation of some areas of the ventricular myocardium, providing the necessary substrate for reentrant arrhythmias.¹⁷⁻¹⁹ The value of programmed ventricular stimulation for identifying patients at risk of sustained ventricular tachycardia (VT) or sudden death has been established in adults with coronary artery disease,^{20,21} but remains controversial in patients with postoperative tetralogy of Fallot.^{5,8,9,19,22,23} The purpose of this study was to analyze prospectively (1) the results of programmed ventricular stimulation in nonselected patients early after surgical repair of tetralogy of Fallot; and (2) the relation between inducible VT and the presence of late potentials or spontaneous ventricular premature complexes (VPCs), or both.

METHODS

Patients: From September 1986 to May 1988, we prospectively studied 31 unselected consecutive patients with tetralogy of Fallot after surgical repair. There were 19 boys and 12 girls (mean age \pm standard deviation 7 ± 4 years, range 1 to 15). Intracardiac repair was performed a mean of 5 months (range 2 to

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38) before the present investigation. All patients were asymptomatic and none had documented or suspected VT before the study.

Body surface and intracavitary signal-averaging:

Recordings were performed using a very high-gain averaging system developed at our institution.¹⁸ The signal is amplified 10^5 to 10^6 times; band-pass filters are set at 100 and 300 Hz (12 dB/octave); the averaging process is performed on 40 consecutive cardiac cycles (end point = residual noise level $<0.5 \mu\text{V}$). The signal-averaged recording (1 to $2 \mu\text{V}/\text{cm}$) is plotted on paper (recording speed 1,000 mm/s) together with a reference electrocardiogram ($200 \mu\text{V}/\text{cm}$). Quantitative assessment includes: (1) total filtered QRS duration (in ms); and (2) measurement of the interval between end of QRS and the point (determined retrogradely) when QRS voltage reaches $40 \mu\text{V}$ (I-40, in ms). End of QRS complex is defined as the point when QRS voltage exceeds twice the value of the baseline noise. Body surface recordings were obtained from 2 bipolar chest leads (between V_2 and V_4 , and V_4 and V_6) using standard silver-chloride electrodes. Recordings were performed at the bedside in a nonshielded room. Intracardiac recordings were obtained from the distal part of electrodes of a quadripolar conventional USCI electrode catheter; recordings were performed at 2 right ventricular sites (apex and outflow tract). For each electrode position, ≥ 3 signal-averaged recordings were obtained to confirm the reproducibility of any abnormal signal detected.

Electrophysiologic study: Electrophysiologic evaluation was performed during postoperative cardiac catheterization. At the time of the study, no patient was receiving antiarrhythmic therapy. Premedication (2 ml solution containing pethidin 50 mg, chlorpromazine 12.5 mg, promethazine 12.5 mg; 0.1 mg/kg body weight, maximum 2 ml) was administered to each patient 60 minutes before beginning of cardiac catheterization. Bipolar intracardiac electrograms were recorded on a multichannel oscillographic recorder (Electronics for Medicine VR-16) and on an ink-jet recorder (Mingograph 82, Siemens), together with 3 surface electrocardiographic leads (I, II and V_1). Right ventricular apical activation time was obtained in all cases to differentiate proximal from distal right bundle branch block.⁶ The programmed ventricular stimulation protocol included (1) single and double premature ventricular stimuli during normal sinus rhythm and during 2 or 3 ventricular paced rhythm (600, 500 and 400 ms); (2) rapid ventricular pacing (minimal cycle length 200 ms); and (3) application of the stimulation protocol both at the right ventricular apex and outflow tract. We did not use 3 or 4 extrastimuli in order to preserve specificity in

asymptomatic patients without documented or suspected VT. The stimuli were 1-ms rectangular pulses, delivered at twice diastolic threshold using a programmable stimulator (Biotronik universal heart stimulator UHS20). The study design was approved by our Ethics Committee of the Department of Pediatrics.

Ambulatory electrocardiographic recording: Twenty-four-hour ambulatory electrocardiographic monitoring was performed in all patients using a 2-channel tape recorder (Del Mar Avionics, model 447) with 2 bipolar chest leads. Tapes were analyzed at 120 times real time using on Avionics Trendsetter II (model 9000A) and the results were manually controlled with samples of electrocardiographic tracings at 25 mm/s when necessary.

Definitions: VENTRICULAR LATE POTENTIALS: abnormal, low-amplitude ($<40 \mu\text{V}$), high-frequency signals appearing at the end of the QRS complex. Late potentials were considered present if the total filtered QRS duration was >140 ms in the presence of right bundle branch block and if the interval between the end of QRS and the voltage $40 \mu\text{V}$ (I-40) was >50 ms.

FRAGMENTED ELECTROGRAMS: electrograms with multiple, high-frequency components lasting >60 ms.^{17,18}

SUSTAINED VENTRICULAR TACHYCARDIA: VTs lasting >30 seconds or requiring direct-current shock because of hemodynamic compromise.

NONSUSTAINED VENTRICULAR TACHYCARDIA: ≥ 3 consecutive VPCs at a rate of >100 beats/min, but self-terminating within 30 seconds.⁵

Statistical analysis: Numerical data were compared using Student's *t* test for unpaired data. Categorical data were compared using chi-square analysis. A *p* value <0.05 was considered statistically significant. Values are expressed as mean \pm standard deviation.

RESULTS

Signal-averaging: Ventricular late potentials were present in 10 patients (32%) (Figures 1 and 2). They were detected from the body surface in 5 (16%), by intracardiac recording in the right ventricular apex in 6 (19%), and by intracardiac recording in the right ventricular outflow tract in 6 (19%). Concordance between body surface and intracavitary recordings is shown in Figure 3: in 1 case late potentials were detected only by body surface recording and in 5 cases only by intracavitary recording. In 4 of 5 patients with body surface negative but intracavitary positive results, the total intracavitary QRS duration including late potentials was shorter than the total filtered QRS duration on the body surface. Patients with late potentials were older, had longer filtered QRS duration, and more often had inducible VT at programmed ventricular stimulation

(Table I) than did those without them. To predict the presence of inducible VT, late potentials had a sensitivity of 100%, a specificity of 75%, a positive predictive value of 30% and a negative predictive value of 100% (overall accuracy 77%).

Programmed ventricular stimulation: In this group of asymptomatic patients, no sustained VT was induced. Nonsustained polymorphic VT (duration 1 to 7 seconds, cycle length 140 to 220 ms) was induced in 3

patients (10%), and 1 or 2 ventricular repetitive responses were observed in 16 additional patients (52%). Nonsustained VT was always induced by application of double extrastimuli (S2, S3) on a driven cycle length <500 ms, at the right ventricular apex (Figure 4). Patients with inducible VT more often had intracavitary late potentials or fractionated local electrograms, and more often had VPCs during Holter monitoring (Table II) than did those without them.

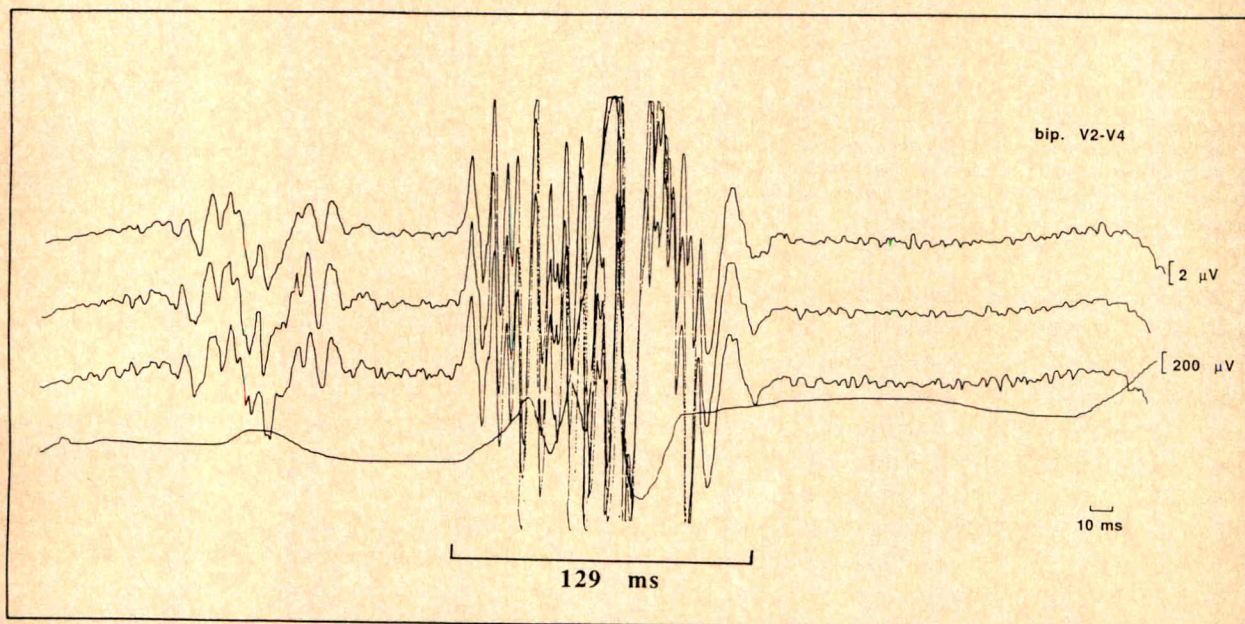


FIGURE 1. Body surface signal-averaging in a 6-year-old child with postoperative tetralogy of Fallot. Three high-gain (2 $\mu\text{V}/\text{cm}$) signal-averaged recordings of 40 consecutive cardiac cycles are displayed together with a reference electrocardiogram (200 $\mu\text{V}/\text{cm}$). Bipolar (bip.) chest lead between V_2 and V_4 ; recording speed 1,000 mm/s; filters 100 and 300 Hz. No ventricular late potentials are seen in this patient. Total filtered QRS duration is 129 ms and I-40 is 31 ms.

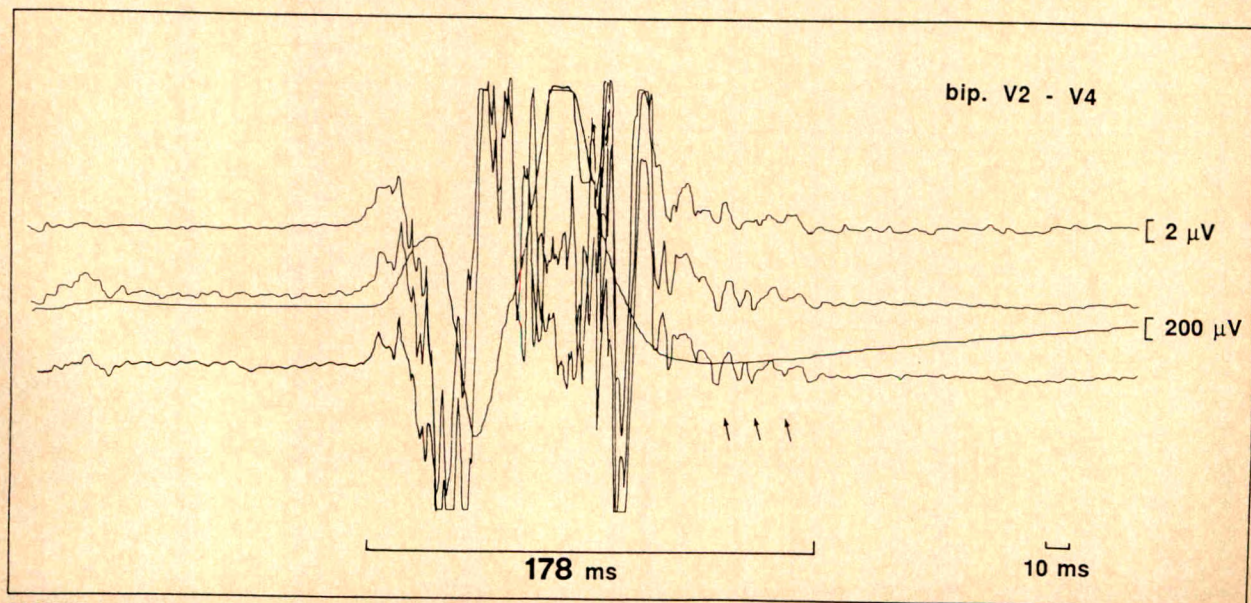


FIGURE 2. Body surface signal-averaging in a 15-year-old child with postoperative tetralogy of Fallot. Three successive high-gain (2 $\mu\text{V}/\text{cm}$) signal-averaged recordings are displayed together with a reference electrocardiogram (200 $\mu\text{V}/\text{cm}$). Bipolar (bip.) chest lead between V_2 and V_4 ; recording speed 1,000 mm/s; filters 100 and 300 Hz. Ventricular late potentials are present (arrows) in this patient. Total filtered QRS duration is 178 ms and I-40 is 90 ms.

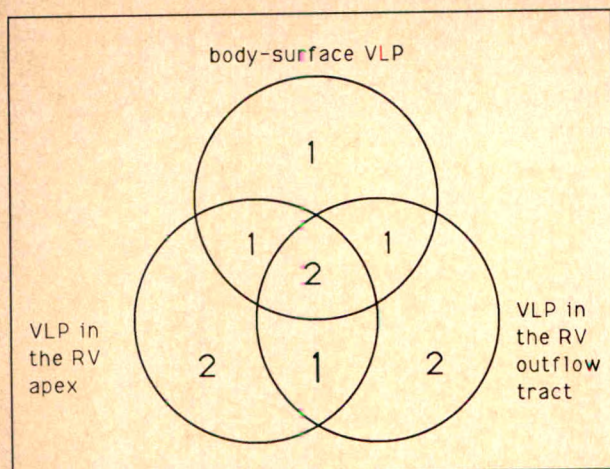


FIGURE 3. Concordance between body surface and intracavitary signal-averaged recordings for the detection of ventricular late potentials (VLP). RV = right ventricular. See text for details.

Electrocardiographic data: On routine 12-lead electrocardiogram, right bundle branch block was found in 30 of 31 patients (97%) and left-axis deviation in 2 patients. During 24-hour Holter monitoring, 12 patients (39%) had ventricular arrhythmias: 9 had infrequent single uniform VPCs, 2 had infrequent multi-form VPCs, and 1 had a single episode of nonsustained VT. Patients with VPCs during Holter monitoring more often had fractionated local electrograms and inducible VT at programmed ventricular stimulation (Table III) than did those without them. To predict the induction of nonsustained VT, the presence of VPCs during Holter monitoring had a sensitivity of 100%, a specificity of 68%, a positive predictive value of 25% and a negative predictive value of 100% (overall accu-

TABLE I Characteristics of Patients With and Without Ventricular Late Potentials

	Late Potentials (n = 10)	No Late Potentials (n = 21)
Mean age (years)	9.7 ± 3.7	5.9 ± 3.8*
Q-RV apex (ms)	30 ± 5	32 ± 14
Fractionated RV apical electrogram	2/10	2/21
Fractionated RVOT electrogram	6/10	7/21
Signal-averaged parameters		
Total QRS in the RV apex (ms)	151 ± 23	125 ± 17 [†]
Total QRS in the RVOT (ms)	156 ± 19	135 ± 24*
Total QRS (body surface) (ms)	152 ± 6	129 ± 18 [†]
Inducible VT	3/10	0/21 [†]
VPCs during Holter monitoring	6/10	6/21
complex VPCs	1/10	2/21
RV systolic pressure (mm Hg)	41 ± 10	48 ± 20
RV-PA pressure gradient (mm Hg)	17 ± 9	18 ± 20

* p < 0.05; [†] p < 0.01.

OT = outflow tract; PA = pulmonary artery; RV = right ventricular; VPC = ventricular premature complexes; VT = ventricular tachycardia.

racy 71%). When the results of Holter monitoring (presence of VPCs) were combined with those of signal-averaging (presence of late potentials), sensitivity remained 100%, specificity increased to 89%, positive predictive value increased to 50% and negative predictive value remained 100% (overall accuracy 90%).

DISCUSSION

Signal-averaging: Late potentials represent delayed activation of small areas of damaged myocardium, and hence the marker for reentrant ventricular arrhythmias.²⁴⁻²⁶ In the present study, late potentials were detected in 32% of asymptomatic patients after surgical repair of tetralogy of Fallot, and their presence was associated with inducible VT during electrophysiologic

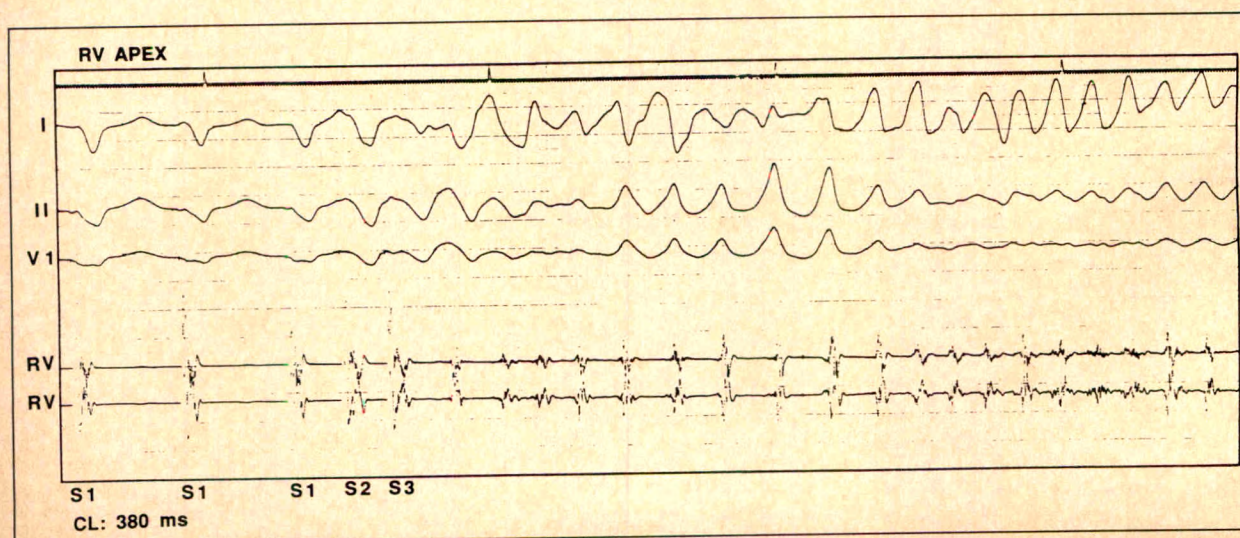


FIGURE 4. Result of programmed ventricular stimulation in an asymptomatic 7-year-old child with postoperative tetralogy of Fallot. The panels are organized from top to bottom with time lines, electrocardiographic leads I, II, V₁ and V₂ intracardiac recordings from the right ventricular apex. Very rapid (cycle length 140 ms) polymorphic ventricular tachycardia was induced by double extrastimulation (S2, S3) during a paced rhythm (cycle length 380 ms), at the right ventricular apex. This arrhythmia was self-terminating after 7 seconds.

TABLE II Characteristics of Patients With and Without Inducible Ventricular Tachycardia

	No Inducible VT (n = 28)	Inducible VT (n = 3)
Mean age (years)	6.9 ± 4.2	9.3 ± 3.2
Q-RV apex (ms)	32 ± 13	28 ± 3
Fractionated RV apical electrogram	2/28	2/3*
Fractionated RVOT electrogram	10/28	3/3†
Ventricular late potentials	7/28	3/3*
Total QRS in the RV apex (ms)	129 ± 18	171 ± 30*
I-40 in the RV apex (ms)	40 ± 12	56 ± 22†
Total QRS in the RVOT (ms)	139 ± 22	170 ± 29†
I-40 in the RVOT (ms)	40 ± 13	61 ± 6*
Total QRS (body surface) (ms)	135 ± 18	155 ± 9
I-40 on the body surface (ms)	41 ± 14	42 ± 17
VPCs during Holter monitoring	9/28	3/3†
complex VPCs	2/28	1/3
RV systolic pressure (mm Hg)	41 ± 10	48 ± 20
RV-PA pressure gradient (mm Hg)	17 ± 9	18 ± 20

* p < 0.01; † p < 0.05.
Abbreviations as in Table I.

TABLE III Characteristics of Patients With and Without Ventricular Arrhythmias During 24-Hour Holter Monitoring

	VPCs (n = 12)	No VPCs (n = 19)
Mean age (years)	7.9 ± 3.5	6.6 ± 4.6
Q-RV apex (ms)	31 ± 11	32 ± 13
Fractionated RV apical electrogram	4/12	0/19*
Fractionated RVOT electrogram	8/12	5/19†
Ventricular late potentials	6/12	4/19
Total QRS in the RV apex (ms)	140 ± 25	129 ± 21
I-40 in the RV apex (ms)	47 ± 14	37 ± 12†
Total QRS in the RVOT (ms)	151 ± 27	136 ± 21
I-40 in the RVOT (ms)	47 ± 6	39 ± 12
Total QRS (body-surface) (ms)	144 ± 18	132 ± 18
I-40 on the body-surface (ms)	43 ± 15	39 ± 13
Inducible VT	3/12	0/19†
RV systolic pressure (mm Hg)	43 ± 13	41 ± 9
RV-PA pressure gradient (mm Hg)	17 ± 12	18 ± 7

* p < 0.01; † p < 0.05.
Abbreviations as in Tables I and II.

testing. These results confirm that late potentials and inducible VT both interrogate the substrate for reentrant ventricular arrhythmias. The right bundle branch block, almost constantly present after surgical repair of tetralogy of Fallot, has systematic effects on the signal-averaged parameters²⁷. Adjustment of definition criteria is mandatory²⁸ and has been made in our study. However, no consensus exists regarding the normal values for the signal-averaged recording in the presence of right bundle branch block, especially if different methods are used. In this study, some isolated cases had late potentials detectable only by intracavitary signal-averaging. These false-negative body surface results are probably due to the prolongation of the QRS complex induced by complete right bundle branch block, which may mask late potentials of short duration.¹⁸ No relation was found between late potentials and spontaneous VPCs during 24-hour Holter monitoring. Similar results have previously been published,¹⁸ and suggest that signal-averaging and Holter monitoring both interrogate different aspects of the arrhythmia, namely the substrate (signal-averaging) and the trigger (Holter recording). To predict the presence of inducible VT, the association of spontaneous VPCs during Holter monitoring and late potentials had a sensitivity of 100%, a specificity of 89%, a positive predictive value of 50% and a negative predictive value of 100% (overall accuracy 90%). Thus, these 2 tests may be used to stratify the risk of serious ventricular arrhythmias after surgical repair of tetralogy of Fallot, and to select cases for invasive electrophysiologic study.

Programmed ventricular stimulation: Several studies have suggested that VT after repair of tetralogy of Fallot are caused by reentry at the site of the previous surgical scar in the right ventricular outflow

tract.^{19,22,23} Programmed ventricular stimulation has been recommended to reproduce clinical arrhythmias and to select effective antiarrhythmic therapy in symptomatic patients.²² However, only few data are available regarding the use of programmed ventricular stimulation in asymptomatic patients after corrective surgery for tetralogy of Fallot. In the present prospective study, conducted early after surgical repair in asymptomatic patients, VT was induced in 10% of the cases. This incidence of inducible VT is comparable to the one reported recently by Chandar et al⁵ in a large group of patients: In that study, inducible VT was present in 9% of asymptomatic patients (23 of 270) and in 45% of patients who had syncope or presyncope (24 of 53). However, several differences exist between our study and the one of Chandar et al: (1) We present a prospective study, whereas the study of Chandar was retrospective. (2) The stimulation protocol was uniform in our patients, whereas it varied among different centers in Chandar's report. (3) Only nonsustained VTs were observed in our study group, whereas half of the inducible VTs in Chandar's report were sustained. This discrepancy may be explained by an older age at the time of surgery, by a longer time interval between operation and the electrophysiologic study, and by the selection of patients. (4) Induced nonsustained VTs were polymorphic in our study, whereas most of them were monomorphic in Chandar's report. This difference may be related to the stimulation protocol rather than to the substrate itself.^{5,20} Although the use of programmed electrical stimulation for identifying patients at risk of sudden death has been established in adults with coronary artery disease,^{20,21} the value of this approach in patients with tetralogy of Fallot after repair has not been established.^{5,19,22,23,29} In fact, in Chandar's report,⁵ none of the 5 patients who died suddenly during follow-up had inducible VT during electrophysiologic

study. This lack of correlation between inducible VT and sudden death may be related to the stimulation protocol or to the various types of induced ventricular arrhythmia. Although Deal et al²² suggested that polymorphic VT may be the harbinger of sudden death in postoperative congenital heart disease, no data support such a conclusion and, at least in adults, induced non-sustained polymorphic VTs are considered as a non-specific response to aggressive stimulation protocols.²⁰ Therefore, further prospective studies are needed to assess the exact prognostic significance of inducible non-sustained VT in postoperative tetralogy of Fallot.

Relation between inducible ventricular tachycardia and spontaneous ventricular premature complexes: In our study, a relation was found between the presence of inducible VT during electrophysiologic study and the presence of spontaneous VPCs during 24-hour Holter monitoring. Conversely, no VT was inducible in asymptomatic patients with a normal 24-hour Holter recording. Similar results have been observed by others,⁵ and it appears that the absence of VPCs during Holter monitoring may be considered as a marker for the patient at low risk of subsequent serious ventricular arrhythmias.

Hemodynamic postoperative status: Our data do not confirm any relation between inducible VT and the postoperative hemodynamic status; no relation was found between the presence of late potentials or spontaneous VPCs during Holter monitoring and an elevated right ventricular systolic pressure. However, only 2 patients in our study had right ventricular systolic pressure >60 mm Hg.

Study limitations: The stimulation protocol included only 2 extrastimuli. Application of 3 or 4 extrastimuli may have increased the frequency of induced VT. The definition of nonsustained VT used in this study is quite sensitive and the exact prognostic significance of induced nonsustained polymorphic VT is unknown.

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Thallium-201 Stress Scintigraphy in Takayasu Arteritis

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Thirty-eight women with Takayasu arteritis were studied using thallium-201 stress myocardial scintigraphy to assess the prevalence and pathophysiology of the perfusion abnormality. Twenty (53%) had abnormal scintigraphic findings (group A). Abnormal scans were divided into 3 groups: permanent defects in 6, reversible defects in 7 and slow washout in 7. The remaining 18 patients had normal scintigrams (group N). Group A had a tendency to be older and to have a high prevalence of complicated significant aortic regurgitation. Interventricular thickness plus left ventricular posterior wall thickness (26 ± 7 vs 17 ± 2 mm, $p < 0.01$) and left ventricular mass (267 ± 121 vs 133 ± 39 g, $p < 0.01$) were all greater in group A on echocardiography. The mean value of the central aortic pressure in systole was 170 ± 15 mm Hg in the 7 catheterized patients in group A. Coronary ostial stenoses were present in 2 group A patients who showed reversible defects on scintigrams. These data indicate that the abnormal perfusion detected by imaging in patients with Takayasu arteritis was responsible for a decrease in coronary reserve or myocardial damage, or both, due to long-standing systemic hypertension or aortic regurgitation. Coronary artery disease should be considered if a reversible defect is present.

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Takayasu arteritis is a nonspecific vasculitis that affects the aorta and its major branches, including coronary and pulmonary arteries.¹ Epidemiologic studies show that Takayasu arteritis is frequent in Asia and South America. This finding leads to the speculation that genetic or racial factors may be involved in Takayasu arteritis.²⁻⁴ In patients with Takayasu arteritis, congestive heart failure or lethal arrhythmias and sudden death are the most frequent causes of death.^{1,5}

It has recently been reported that, in addition to coronary artery disease, several other heart diseases may result in thallium perfusion abnormalities. Several investigations have been conducted on cardiac involvement in Takayasu arteritis by using cardiac catheterization or echocardiography.⁶⁻⁸ Our objective was to investigate the myocardium of patients with Takayasu arteritis using thallium-201 stress scintigraphy.

METHODS

Patients: Thirty-eight women ranging in age from 24 to 72 years comprised the group with Takayasu arteritis. In all patients, the diagnosis of Takayasu arteritis was established by clinical and angiographic data.⁹ Patients continued to receive their usual medical treatment throughout the study.

Thallium-201 imaging: Thirty-eight patients underwent thallium-201 stress myocardial scintigraphy.^{10,11} Of these, 27 exercised on an upright bicycle ergometer. The remaining 11 older or "pulseless" patients received an infusion of dipyridamole.

EXERCISE: Exercise testing was performed with a multistage bicycle ergometer using the symptom-limited method. The work load, which began at 25 W, was increased by 25 W every 3 minutes. Exercise continued for 1 minute after the intravenous injection of 111 MBq of thallium-201 at the end point. Exercise was discontinued when patients developed angina, ischemic ST depression on the electrocardiogram, serious arrhythmia, dyspnea or leg fatigue. The 12-lead electrocardiogram was monitored during exercise and blood pressure recorded every 3 minutes.

DIPYRIDAMOLE: After the intravenous infusion of dipyridamole (0.568 mg/kg) for 4 minutes, patients received an intravenous injection of 111 MBq of thallium-201. The electrocardiogram and blood pressure were monitored as during the previous exercise testing.

THALLIUM-201 EMISSION COMPUTED TOMOGRAPHY: Acquisition of thallium images was begun immediately after exercise or 9 minutes after the dipyridamole infusion. Patients were imaged using a rotational gamma camera (Hitachi RC150DT) equipped with a low-energy, all-purpose parallel hole collimator. A total of 32 projections were obtained for 30 seconds in a 180° arc extending from the 45° right anterior oblique to the left posterior oblique projection. A 20% energy window was centered on the 80-keV x-ray peak. All projections were stored on a magnetic disk using a 64 × 64, 16-bit computer matrix.

After correction for nonuniformity and center of rotation, contiguous transaxial tomograms encompassing the entire heart were reconstructed after filtered back projection with a Chesler filter. Then, using the left ventricular long axis as a reference, the images were constructed into short-axis, horizontal long-axis and vertical long-axis tomograms (oblique images). Delayed images were acquired and constructed in the same projections 3 hours later. Both during stress and at redistribution, each short-axis cut was divided into 60 segments of 60 equidistant radii. Maximal count circumferential profiles for each cut were then generated from the apical to the basal cut. The values were then normalized to the highest value found in each slice and expressed as a circumferential profile curve to represent myocardial thallium distribution. Similarly, the thallium washout rate of each myocardial segment of the entire left ventricle was calculated and plotted as the washout rate curve: washout rate = (initial count-delayed count/initial count) × 100. Permanent and reversible defects were distinguished by evaluation of both visual inspection and the quantification of the circumferential profiles. Slow washout was defined as falling below the lower limit of normal without any defects on stress. Tomographic images were interpreted by consensus of 2 observers who had no knowledge of the clinical findings.

Scalar (12-lead) electrocardiography: Supine, resting 12-lead electrocardiograms were examined in the 38 patients on the day of scintigraphy. Electrocardiographic left ventricular hypertrophy was defined by the Romhilt-Estes criteria. Myocardial ischemia was defined as >0.1 mV of ST depression in V₅ or V₆.

Echocardiographic studies: Echocardiographic data were obtained from a commercially available imaging system with Doppler capability (Toshiba SSH-160A equipped with a 2.5- or 3.75-MHz transducer). Two-

dimensional images oriented the ultrasonic beam for the best M-mode recordings of the left ventricles. Measurements of left ventricular end-diastolic and end-systolic dimensions, and wall thickness (interventricular septal thickness + left ventricular posterior wall thickness) were performed from M-mode echocardiograms. Technically adequate recordings were obtained in 33 of the 38 patients (87%). Left ventricular mass was obtained using the formula of Devereux et al.¹² The severity of aortic regurgitation was assessed by the flow mapping technique on conventional pulsed and color Doppler echocardiography.

Cardiac catheterization: Cardiac catheterization and coronary cineangiography were performed in 9 patients using standard techniques.

Statistical analysis: Data were compared using Fisher's exact test or the unpaired *t* test. Statistical significance refers to a *p* value <0.05.

RESULTS

Thallium-201 emission computed tomography:

Scintigraphic abnormalities were identified in 20 of the 38 patients (53%) with Takayasu arteritis. Permanent defects were observed in 6 patients (Figure 1), reversible defects in 7 (Figure 2) and slow washout in 7. The differences between patients with perfusion abnormalities (group A) and those with normal scintigrams (group N) were then compared.

Comparison of group A versus B (Table I): AGE: The mean age of group A was 48 ± 13 (mean ± standard deviation) years and that of group N was 41 ± 8 years. Group A tended to be older but not to a statistically significant extent. There was no significant difference in body surface area between the 2 groups.

ELECTROCARDIOGRAMS: Left ventricular hypertrophy or ischemic ST depression was evident in 13 group A (65%) and in 2 group B (11%) patients. Electrocardiographic abnormalities were significantly more frequent in group A than in group N (*p* <0.01).

M-MODE ECHOCARDIOGRAPHIC DATA: Wall thickness (26 ± 7 vs 17 ± 2 mm, *p* <0.01) and left ventricular mass (267 ± 121 vs 133 ± 39 g, *p* <0.01) were significantly greater in group A than in group N (Figure 3). These echocardiographic data suggest that the group A patients had left ventricular hypertrophy with normal contractility.

PRESENCE OF AORTIC REGURGITATION: Eight of the 20 group A patients (40%) had significant aortic regurgitation, whereas only 3 of the 18 group N patients (17%) had this complication. However, the difference was not statistically significant.

PRESSURE OF THE ASCENDING AORTA (CENTRAL AORTIC PRESSURE): Cardiac catheterization was conducted in 7 group A patients, 5 of whom had significant aortic re-

gurgitation. The mean value of the central aortic pressure in group A was 170 ± 15 mm Hg in systole and 60 ± 13 mm Hg in diastole.

CORONARY ARTERY LESIONS: We were able to examine coronary artery stenoses in 8 group A and 2 group N patients. This lesion was diagnosed in 2 group A patients at autopsy. Significant stenoses were present in only 2 of the subjects in group A. One, a 72-year-old woman, had a 99% diameter stenosis of the right coronary artery.

ostium and a 75% diameter stenosis of the left anterior descending artery. The other, a 53-year-old woman, had a 99% diameter stenosis of the right coronary ostium. These ostial stenoses were thought to reflect the coronary involvement of Takayasu arteritis.

Mortality: The 2 patients in group A died suddenly during the study. The cause of death was thought to be ventricular arrhythmia.

DISCUSSION

The usefulness of evaluating ischemic heart disease by thallium-201 stress scintigraphy has been established. It has been reported that several heart diseases, in addition to coronary artery disease, have abnormal scintigraphic findings.¹³⁻¹⁸

Pfisterer et al¹³ reported that 12 of 17 patients with predominant aortic regurgitation had distinct left ventricular apical defects during exercise despite normal coronary arteries. They concluded that changes in left ventricular geometry and contraction pattern by volume overload might cause perfusion abnormalities.¹⁹

Schulman et al¹⁴ performed stress imaging in hypertensive patients, and found that 29% of those with a low risk of coronary disease had abnormal thallium-201

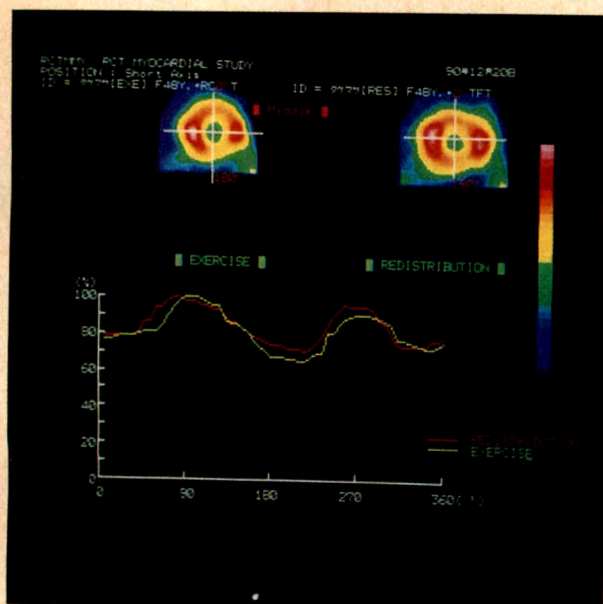


FIGURE 1. Stress (left) and redistribution (right) images obtained in a 48-year-old woman with normal coronary arteries. The short-axis images and the circumferential profile curves (bottom) obviously demonstrated a permanent defect in the anteroseptal wall.

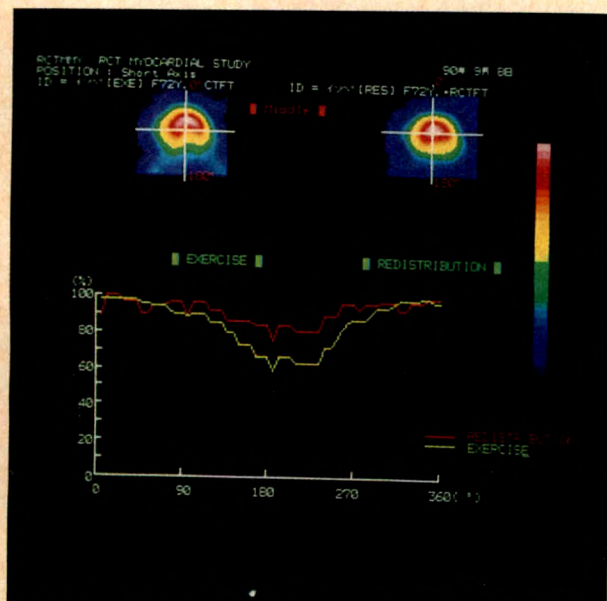


FIGURE 2. Stress (left) and redistribution (right) images obtained in a 72-year-old woman with a 99% diameter stenosis of the right coronary ostium. The short-axis images and the circumferential profile curves (bottom) show a typical reversible defect in the inferoposterior wall.

TABLE I Comparison of Group A and Group N

	Group A	Group N
LVH or ischemic ST change on ECG (n = 38)	13*	2
Echocardiographic parameters (n = 33)		
LVDd (mm)	46 ± 6	44 ± 5
LVDs (mm)	28 ± 6	27 ± 4
%FS (%)	39 ± 7	39 ± 6
WT (mm)	26	17 ± 2
LVM (g)	267 ± 121*	133 ± 39
Aortic regurgitation (n = 38)	8	3
Hemodynamics (n = 7)		
sAoP (mm Hg)	170 ± 15	—
dAoP (mm Hg)	60 ± 13	—
LVEDP (mm Hg)	14 ± 4	—

* p < 0.01.

ECG = electrocardiogram; %FS = percent fractional shortening; LVDd = left ventricular end-diastolic dimension; LVDs = left ventricular end-systolic dimension; LVEDP = left ventricular end-diastolic pressure; LVH = left ventricular hypertrophy; LVM = left ventricular mass; sAoP & dAoP = central aortic pressure in systole and in diastole; WT = interventricular thickness plus ventricular posterior wall thickness.

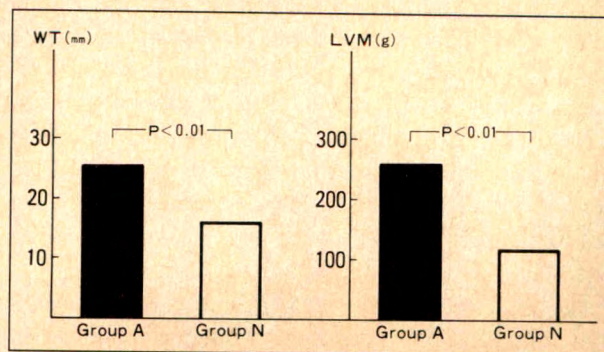


FIGURE 3. Wall thickness (WT) and left ventricular mass (LVM) were significantly greater in group A than in group N.

stress images. They considered the possibility that undetected coronary artery disease, an increased oxygen demand caused by increased left ventricular mass and inadequate coronary reserve may be related. O'Gara et al¹⁵ found that 41 of 72 patients (57%) with hypertrophic cardiomyopathy demonstrated abnormalities in myocardial perfusion on thallium-201 emission computed tomography. Their patients were considered to be free of coronary artery disease. They concluded that myocardial ischemia in hypertrophic cardiomyopathy may result from one or more mechanisms, including an inadequate capillary density relative to the increased myocardial mass, impaired left ventricular relaxation, or abnormalities of the small intramyocardial coronary arteries. Positive scintigraphic scans were demonstrated by von Dohlen et al¹⁶ in 11 of 28 subjects (38%) with hypertrophic cardiomyopathy, despite normal epicardial coronary arteries. In their patients, left ventricular wall thickness was greater, left ventricular ejection fraction was lower and ventricular tachycardia was more frequent in those with thallium perfusion abnormalities than in those with normal scans. These investigators confirmed that myocardial ischemia, myocardial fibrosis, or both, were responsible for the abnormalities.

We observed that 20 of our 38 patients (53%) with Takayasu arteritis had a perfusion defect or a slow washout. Electrocardiographic abnormalities were more frequent in group A than group N. Wall thickness and left ventricular mass were greater in group A than group N. Complicated significant aortic regurgitation tended to be more common in group A than group N. The sites of the perfusion abnormalities are shown in the various portions of the left ventricle. We could not adequately examine the correlation between perfusion abnormalities and epicardial coronary artery disease, including ostial stenosis. It was reported that about 10% of patients with Takayasu arteritis had coronary artery involvement.¹ Coronary lesions were found in 2 of the 8 patients in group A: 1 had a 99% diameter stenosis of the right coronary ostium and the other had a 99% diameter stenosis of the right coronary ostium with a 75% diameter stenosis of the left anterior descending artery. Both patients had reversible defects in areas of the right coronary artery. Peripheral blood pressure often cannot be measured adequately in patients with Takayasu arteritis because of stenotic or occlusive lesions of the major aortic branches. One should obtain the central aortic pressure to evaluate the afterload to the left ventricle. Nevertheless, in our patients, we could not obtain adequate pressure data. The mean central aortic pressure in systole in the 7 group A patients was 170 mm Hg. We believe that systemic hypertension plays an important role in the development of left ventricular impairment.

It is reasonable to think that abnormal scintigraphic findings are responsible for a decrease in coronary reserve, myocardial damage, or both, due to long-standing systemic hypertension or to aortic regurgitation. On the other hand, an epicardial or ostial coronary lesion should be considered when a typical reversible defect is revealed. There are a few cases of Takayasu arteritis with myocarditis.²⁰ In >10 cases autopsied, however, we have not seen any evidence of myocarditis.

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Usefulness of Dipyridamole-Handgrip Echocardiography Test for Detecting Coronary Artery Disease

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Dipyridamole-echocardiography testing has been proposed for the diagnosis of coronary artery disease (CAD). It is a feasible, safe, highly specific and relatively inexpensive diagnostic test. The major limitation of the dose used (0.56 mg/kg within 4 minutes) as a test is a relatively low sensitivity.¹ Several methods have been proposed to overcome this limitation, including combination with dynamic exercise² and the use of a higher dosage of dipyridamole.³ Another attractive means of increasing the sensitivity of this test would be handgrip exercise, which is a weak stressor when used alone.⁴ Although handgrip exercise reportedly only slightly increased the sensitivity of the dipyridamole-echocardiography test⁵ in a study that used a 25% maximal grip strength over 4 minutes, according to the protocol previously used for thallium testing,⁶ a more strenuous handgrip stress can conceivably apply a greater ischemic challenge to the myocardium by inducing more profound hemodynamic changes. The aim of this study was to assess whether a strong handgrip stress (50% of predetermined maximal grip strength until exhaustion or up to 5 minutes) might increase the sensitivity of dipyridamole-echocardiography testing for CAD detection.

An initial set of 59 in-hospital patients undergoing diagnostic coronary angiography for history of chest pain was initially considered. We excluded patients with congenital heart disease, valvular heart disease, ventricular hypertrophy, severe arrhythmias and conduction defects. The quality of 2-dimensional echocardiographic imaging at rest was not considered sufficient for adequate wall motion analysis for 6 patients (10%) who were therefore excluded from further investigations.

The remaining 53 patients, 48 men and 5 women, aged 37 to 66 years (mean 55), were enrolled in the study. Of these, 35 had a history of myocardial infarction.

Patients in whom no transient asynergy of myocardial contraction occurred during dipyridamole-echocardiography testing underwent the dipyridamole-handgrip echo test.

No patient was receiving antianginal therapy while undergoing coronary angiography and stress tests.

Dipyridamole (Curantyl™, fa Arzneimittelwerk, Dresden) was infused intravenously at a dose of 0.75 mg/kg in 100 ml of 5% glucose within an 8-minute period (half the dose during the first 3 minutes and the second half during another 5-minute interval). Twelve-lead electrocardiography and cuff blood pressure were monitored during every minute of procedure.

Two-dimensional echocardiography was continuously performed during dipyridamole infusion and up to 10 minutes afterward. Every positive test was terminated with 240 mg of aminophylline administered intravenously.

In cases of an inconclusive pharmacologic test, isometric handgrip using 50% of predetermined maximal grip strength was applied (after a 4-minute pause) until exhaustion (the longest interval was 5 minutes in our series). Patients were followed according to the same protocol as in the pharmacologic test. The timing of events is shown in Figure 1.

Two-dimensional echocardiography continuously recorded on videotape during the tests was performed from 2 apical views (apical 4-chamber and apical long-axis) with a commercially available mechanical scanner system (MK 600, Advanced Technology Laboratories, U.S.A., 3-MHz transducer). Wall motion was qualitatively graded as normal, hypokinetic, akinetic or dyskinetic.^{1,2}

Positivity of the test was based on the detection of a transient asynergy of contraction, absent or of a lesser degree in the baseline examination. In patients with a previous myocardial infarction, the higher degree or extent of the preexisting contraction abnormality as well as the occurrence of remote asynergy indicated a positive result.

All standard echo views were examined while patients were at rest. Every observed new asynergy was localized by repeated imaging of apical 4-chamber and long-axis views during the study. All echo studies were performed and interpreted by a cardiologist blinded to angiography.

Routine cineangiography using the Judkins technique in multiple projections was performed within 1

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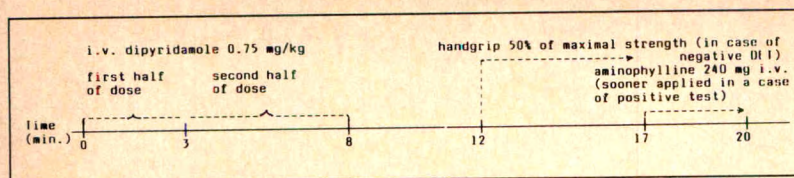


FIGURE 1. Time course of experimental protocol. DET = dipyridamole echo test; i.v. = intravenous.

week after stress tests. No significant changes in clinical condition occurred within this period.

A luminal narrowing $>70\%$ in ≥ 1 major coronary vessel was considered as significant coronary artery stenosis.

Continuous data are expressed as mean \pm standard deviation. Differences between results of single pharmacologic and combined echo tests were compared by testing of confidence limits.

At coronary angiography, 40 patients had significant and 13 had nonsignificant CAD. The sensitivity and specificity of single dipyridamole-echocardiography testing was 53 and 100%, respectively. With the addition of handgrip testing, overall sensitivity increased from 53 to 78% ($p < 0.001$), with no decrease in specificity (100%). "Late positivity" of the dipyridamole effect only cannot be completely eliminated but, as it is rare, it could not influence the results of the combined test significantly. A comparison of the results of the echocardiography and the handgrip exercise stress tests as they relate to significant CAD is shown in Figure 2.

Values of the rate-pressure product increased to 130% after dipyridamole infusion, compared with values at rest. As blood pressure tended to decrease slightly with dipyridamole, the overall increase of the rate-pressure product can be mostly attributed to the increase in heart rate.

With the addition of the handgrip stress test, the values of the rate-pressure product doubled values at rest, mainly because of the increase in blood pressure, whereas the change in heart rate was less pronounced.

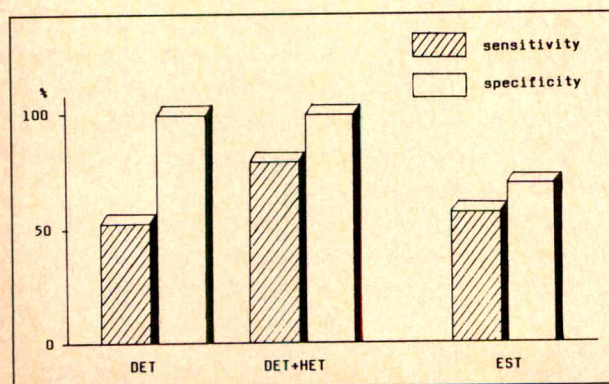


FIGURE 2. Noninvasive detection of $>70\%$ coronary artery stenosis on coronary angiography. DET = dipyridamole echo test; EST = exercise stress test; HET = handgrip echo test.

The values of hemodynamic parameters measured during stress testing are listed in Table I. There was a significant difference in the rate-pressure product between dipyridamole-echocardiography and dipyridamole-handgrip echo tests in all patients (disjunctive 95 percent confidence intervals for mean). Similar differences in the rate-pressure product (123 ± 24 vs 180 ± 42 , $p < 0.01$) were also found at the onset of ischemia of the single pharmacologic versus the combined dipyridamole-handgrip test in all positive studies.

No serious side effects were observed during the stress tests. Transient headache and flush appeared in 12 patients (23%) during dipyridamole infusion. All the symptoms, including chest pain in the case of positive tests, disappeared immediately after aminophylline injection. No side effects related to handgrip test were recognized.

The quality of echocardiographic images remained unchanged during both tests.

In our study, dipyridamole-handgrip echo testing revealed transient myocardial ischemia in 10 of 19 patients with significant CAD, in whom diagnosis would have been missed by dipyridamole-echocardiography alone. This marked rise in sensitivity took place without any loss in feasibility, safety and specificity, outlining a possible practical role for dipyridamole-handgrip testing in the accurate noninvasive diagnosing of CAD.

Significant differences in the rate-pressure product at the onset of ischemia in the single pharmacologic versus the combined test, together with nonsignificant differences between these 2 groups irrespective of the severity of stenotic lesion, probably express that the combined test detected milder forms of ischemia, from the point of view of function, but not anatomy.

TABLE I Hemodynamic Findings in the 32 Study Patients Undergoing Dipyridamole-Echocardiography and Dipyridamole-Handgrip Echocardiography Tests

	Rest	DET	D-HET
Heart rate (beats/min)	72 \pm 11	96 \pm 13	106 \pm 16
Systolic blood pressure (mm Hg)	144 \pm 17	131 \pm 16	175 \pm 25
Rate-pressure product ($\times 1/100$) (beats/min \times mm Hg)	103 \pm 19	126 \pm 23	186 \pm 45

Data are expressed as mean \pm standard deviation. As all 95% confidence intervals for mean are disjunctive for all parameters involved, the results of the Kruskal-Wallis test are $p < 0.001$.
DET = dipyridamole-echocardiography test; D-HET = dipyridamole-handgrip echo test.

Theoretically, handgrip stress testing—when superimposed on dipyridamole infusion—could provoke myocardial ischemia through ≥ 2 different mechanisms: an increase in myocardial oxygen demand or a decrease in supply.⁵ Dipyridamole does not block the hemodynamic response to handgrip testing.^{6,7} The peak rate-pressure product (an established index of cardiac work) achieved after dipyridamole-handgrip testing was significantly higher than after dipyridamole alone. With regard to blood supply, it has been documented that dipyridamole causes a slight to mild reduction in coronary arterial vasomotor tone, but it does not prevent the coronary constrictor effect of handgrip testing.⁸ In the presence of increased rates of flow (induced by dipyridamole), the handgrip-induced increase in epicardial coronary stenoses might detrimentally potentiate the dynamic coronary stenosis and thus markedly raise the transstenotic gradient present at rest. Finally, the increase in left ventricular end-diastolic pressure induced by handgrip testing reduces perfusion (by increasing extravascular resistance) and increases oxygen demand (by increasing the wall stress).

Our results are only apparently in disagreement with those of others³ who report only a 7% increase in sensitivity when comparing the dipyridamole-handgrip echo test to dipyridamole alone. Some differences in the study protocol may well explain these discrepancies. First, we used a larger dipyridamole dose (0.75 mg/kg over 8 minutes instead of 0.56 mg/kg over 4 minutes), which may guarantee a more sustained and prolonged coronary

vasodilation. Second, we applied a more strenuous handgrip stress (50 vs 25% of predetermined maximal grip strength).

Therefore, sufficiently severe isometric exercise testing can be conveniently combined with the dipyridamole-echocardiography test, because it sharply increases the sensitivity of the test with no apparent decrease in safety, feasibility and specificity.

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Comparison of Manual Versus Automated Edge Detection for Determining Degrees of Luminal Narrowing by Quantitative Coronary Angiography

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The known inaccuracies in visual angiographic interpretation¹ have led to the development of many quantitative methods for determining absolute coronary arterial dimensions. The use of automated edge detection reduces the bias inherent in visual interpretation and improves precision and accuracy. The comparability of measurements obtained with automated versus eye-hand edge-detection techniques and differ-

ent processing algorithms is not known. Accordingly, we compared the 2 most widely used methods: manual (eye-hand) edge detection versus the automated edge-detection method.

Forty-two angiograms meeting the following criteria were selected for analysis: (1) adequate visualization of a single coronary lesion in 2 orthogonal projections (i.e., 30° right anterior oblique, 60° left anterior oblique); (2) absence of intraluminal thrombus; and (3) adequate gray scale and line-pair resolution (> 2.6 line-pair/mm). Thirty patients had stable angina and were referred for percutaneous transluminal coronary angioplasty; 12 patients had normal coronary arteries.

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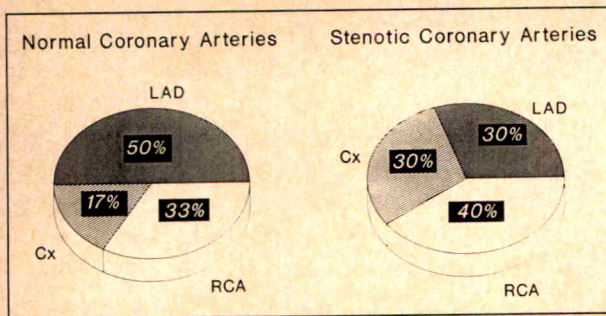


FIGURE 1. Distribution of vessels studied in patients with normal coronary arteries ($n = 12$) and in patients with stenotic coronary arteries ($n = 30$). Cx = circumflex artery; LAD = left anterior descending artery; RCA = right coronary artery.

The identical arterial segment was analyzed in 2 orthogonal projections using both methods; only 1 segment per vessel was analyzed in each angiogram and only 1 frame per projection was analyzed. If possible, the 2 orthogonal views were analyzed in the same part of the cardiac cycle with the specific preference for end diastole.

The method of manual (eye-hand) edge detection (Brown-Dodge Method) has been described in detail elsewhere.² Briefly, the angiographic frame was projected vertically onto a rectilinear grid at 5 \times magnification. An outline of the angiographic catheter (7Fr or 8Fr) was traced. The arterial segment under study was outlined and a reference point common to both projections was identified (for spatial matching of the orthogonal projections). The traced vessel segments were then digitized and transmitted by telephone modem to the VAX750 computer at the University of Washington, Seattle. The traced outline was corrected for pincushion distortion (from a previously entered file specific to each x-ray unit) and out of plane distortion, as well as for magnification. Orthogonal views

TABLE I Comparison of Normal Coronary Arteries ($n = 12$)

	Brown-Dodge Method	Reiber-CAAS Method	Mean Difference (Reiber-CAAS vs Brown-Dodge)
Diameter stenosis (mm) (LAO view)	3.04 ± 0.71	3.18 ± 0.75	0.14 ± 0.25
Diameter stenosis (mm) (RAO view)	2.87 ± 0.76	3.03 ± 0.76	$0.16 \pm 0.25^*$
Cross-sectional area (mm^2)	7.72 ± 3.61	8.05 ± 3.68	0.33 ± 0.74

* $p < 0.05$.

CAAS = Coronary Angiography Analysis System; LAO = left anterior oblique view; RAO = right anterior oblique view.

were then matched, using the reference point, along the entire length of the artery. Calculation of arterial cross-sectional area was calculated at each point along the centerline and the area of the normal segment was calculated at a user-defined point.

The method of automated edge detection (Reiber-Coronary Angiography Analysis System [CAAS]) has been described in detail by Reiber et al³ and was performed using the CAAS (CAAS, PIE Medical, Maastricht, Belgium). A cine frame from each view was digitized directly from film to a matrix of approximately $1,000 \times 1,500$ pixels. The outline of the angiographic catheter was determined using a semiautomated edge-detection algorithm with correction for pincushion distortion. The arterial contour detection was similarly performed by an automated algorithm using a user-identified and computer-smoothed centerline. The mean and minimal diameters of each segment were calculated. The diameter of a normal segment was determined at the user-defined point as previously described. Because no bi-plane matching was performed, the minimal area of the stenosis was calculated manually according to

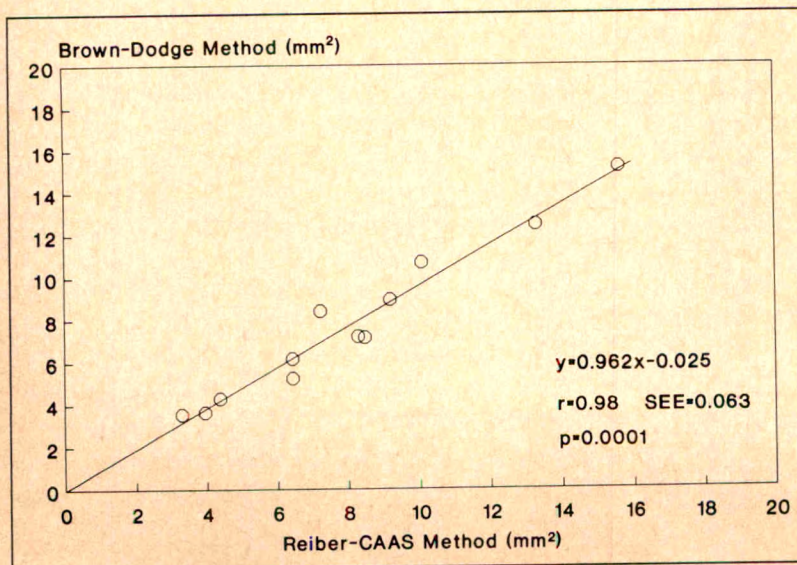


FIGURE 2. Comparison between the 2 methods of cross-sectional area (mm^2) in normal coronary arteries ($n = 12$). CAAS = Coronary Angiography Analysis System; SEE = standard error of the estimate.

the equation: π (minimum diameter, right anterior oblique)(minimum diameter, left anterior oblique)/4.

All results are calculated as mean \pm 1 standard deviation. The comparison between the 2 methods was performed using linear regression analysis and paired t test. Statistical significance was assumed at $p < 0.05$.

Among the 42 patients studied, the artery analyzed was left anterior descending in 15 patients, right coronary artery in 16, and circumflex in 11 (Figure 1). For all segments analyzed, diameter ranged from 0.46 to 4.76 mm and cross-sectional area from 0.25 to 15.61 mm².

The comparison of measurements obtained in 12 patients with normal coronary arteries is listed in Table I and shown in Figure 2. Measurements of arterial cross-sectional area using each method were closely correlated. However, the diameter measurements in the right anterior oblique projection were slightly but significantly greater when assessed using the Reiber-CAAS method (Table I). The diameter measurements in the left anterior oblique projection were similar between methods.

The comparison of arterial stenosis in 30 patients with stable angina before percutaneous transluminal coronary angioplasty is listed in Table II and shown in Figure 3. The diameters of the normal segment and minimal lesion diameters measured using both methods were highly correlated and not significantly different (Figure 3). Similarly, there was no difference in the measurement of cross-sectional area between the 2 methods (Table II).

These data indicate that, in the absence of intracoronary thrombus and recent percutaneous transluminal coronary angioplasty, absolute coronary dimensions obtained over a broad range of measurements are similar using the quantitative methods of Brown-Dodge and

TABLE II Comparison of Arterial Stenosis (n = 30)

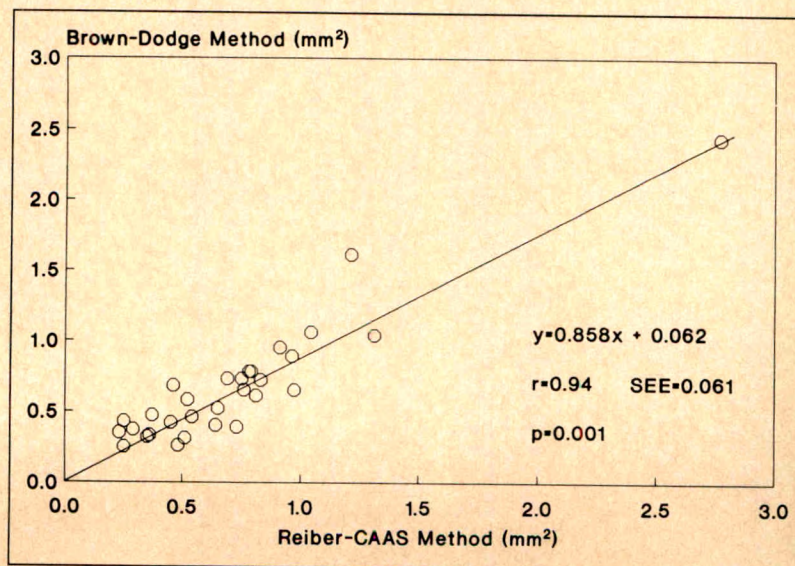
	Brown-Dodge Method	Reiber-CAAS Method	Mean Difference (Reiber-CAAS vs Brown-Dodge)
Diameter stenosis (mm) (LAO view)	0.92 \pm 0.33	0.96 \pm 0.36	0.04 \pm 0.12
Diameter stenosis (mm) (RAO view)	0.87 \pm 0.28	0.93 \pm 0.29	0.06 \pm 0.18
% Diameter stenosis (LAO view)	71 \pm 9	70 \pm 10	1.2 \pm 3.7
% Diameter stenosis (RAO view)	68 \pm 11	67 \pm 10	1.2 \pm 8.2
Cross-sectional area (mm ²) of stenosis	0.68 \pm 0.44	0.72 \pm 0.48	0.04 \pm 0.17

Abbreviations as in Table I.

Reiber-CAAS. Additionally, in a large number of vessels, the minimal cross-sectional area measured using the Brown-Dodge method with biplane matching was similar to that obtained from orthogonal, single-plane measurements without spatial biplane matching (Reiber-CAAS method). These findings suggest that automated arterial contour edge detection produces results similar to human eye-hand edge detection and that biplane matching usually has minimal benefit. Consequently, measurements and data analysis obtained with these 2 frequently used methods should be interchangeable.

There was a trend for arterial diameters measured with Reiber-CAAS to be greater than those measured with the Brown-Dodge system; the difference reached statistical significance only for the diameter stenosis in the right anterior oblique view for comparison of normal coronary arteries (Table I). The difference may have resulted from lack of out-of-plane magnification correction in Reiber-CAAS system or differences in the algorithms used. Overall, the differences observed were so

FIGURE 3. Comparison between the 2 methods of minimum cross-sectional area (mm²) in stenotic coronary arteries (n = 30). Abbreviations as in Figure 2.



small that they may be considered trivial from the clinical point of view.

Several caveats should be considered in the comparison of these 2 methods. First, we excluded thrombotic coronary lesions and those after percutaneous transluminal coronary angioplasty because edge detection by any method is known to be inaccurate in this setting.⁴ Therefore, interchangeability of these methods should not be extended to thrombotic or "unstable" lesions.

Second, we analyzed angiograms that we considered adequate for quantitative analysis. Substandard angiographic lesion definition might lead to divergent measurements with each edge-detection system. However, angiograms of poor quality should not be quantitatively analyzed because the measurements may be inaccurate regardless of the method of quantitative analysis used.

Third, we only analyzed angiograms from 42 patients. It is possible that, in extreme instances, out-of-plane magnification might be inordinately large and result in significant measurement error.

Fourth, the selection of patients as those suitable for angioplasty may have resulted in selection bias so that coronary artery lesions with mostly concentric stenosis were chosen. It is possible that in the case of eccentric stenosis, the calculation of minimal cross-sectional area from the minimal diameters in 2 views might be less accurate than that obtained from biplane-matched diameters.

Quantitative coronary angiography has become a necessary tool in clinical research that pertains to the angiographic assessment of coronary artery disease. Furthermore, specific measurements based on the use of

quantitative coronary angiography have been proposed that are of clinical and physiologic importance.^{5,6} The clinical implication of this study is that in the absence of intracoronary thrombus, absolute coronary dimensions obtained over a broad range of measurements in different laboratories using eye-hand (Brown-Dodge method) and automated edge-detection (Reiber-CAAS method) techniques are directly comparable.

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Multiple Accessory Pathways in the Wolff-Parkinson-White Syndrome as a Risk Factor for Ventricular Fibrillation

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Ventricular fibrillation (VF) after atrial fibrillation is the mechanism of sudden death in most patients with Wolff-Parkinson-White (WPW) syndrome.¹⁻³ Initial data from Duke University¹ suggested that patients who had VF had a shortest RR interval between preexcited beats during atrial fibrillation <250 ms. The use of the shortest RR interval during atrial fibrillation in predicting sudden death prospectively is, however, limited by its low positive predictive value.⁴ Several studies^{1,5} have also noted the increased frequency of multiple accessory pathways in VF patients with WPW syndrome although other investigators⁶ suggested that this was not the case. We sought to determine whether VF occurs more frequently in patients with multiple accessory pathways and whether multiple pathways may be considered as an additional risk factor for this complication.

The study group comprised all patients with manifest preexcitation in whom a complete electrophysiologic study and an operative ablation of the accessory pathway were performed at University Hospital, London, Ontario, from June 1982 to June 1990. We used a surgical population because intraoperative confirmation of multiple accessory pathways was available. The techniques of electrophysiologic testing at University Hospital,⁷ intraoperative mapping⁸ and surgical ablation⁹ have previously been described.

Multiple accessory pathways were defined when they occurred in >1 of the 4 major surgically defined areas. These were left lateral, posteroseptal, right free wall and right anteroseptal. Multiple accessory pathways were also considered present if there were 2 areas of preexcitation separated by at least a 2-cm distance and an intervening area with slower activation time. VF was considered to have occurred secondary to atrial fibrillation if it was documented electrocardiographically or if it occurred in the absence of

any cardiac disease potentially associated with this complication.

Standard definitions for sensitivity, specificity and predictive accuracy were used.⁴ Patients with a history of VF were considered to be "true positives" for sudden death. Student's unpaired *t* test was used to determine the statistical difference seen in continuous variables. Univariate analysis of discrete variables was performed using a chi-square test. Multivariate stepwise logistic regression was used to examine the risk factors associated with VF. The variables examined were age, sex, multiple accessory pathways, shortest RR interval between preexcited beats during atrial fibrillation and the anterograde effective refractory period of the accessory pathway. The variables examined were then removed sequentially from the analysis if the *p* value was >0.1. A probability <0.05 was considered significant. Group data are expressed as mean \pm 1 standard deviation.

There were 251 patients, of whom 31 (12.4%) had multiple accessory pathways and 18 (7.2%) had a history of VF. The patients with multiple accessory pathways, when compared with patients with single accessory pathways (Table I), were younger at the time of surgery (25.2 ± 10.7 vs 33.0 ± 12.4 years, *p* = 0.001) and presented more frequently with documented atrial fibrillation (51.6 vs 29.1% , *p* = 0.01) and VF (16.1 vs 5.9% , *p* = 0.04). At electrophysiologic study, a shorter average RR interval during atrial fibrillation (319.1 ± 59.6 vs 349.2 ± 72.2 ms, *p* = 0.04), the presence of preexcited reentrant tachycardia (45.2 vs 20% , *p* = 0.003) and a shorter anterograde effective refractory period of the accessory pathway (256.1 ± 38.1 vs 273.8 ± 28.2 ms, *p* = 0.007) distinguished patients with multiple accessory pathways from patients with single accessory pathways. The difference in the shortest RR interval (214.3 ± 48.3 vs 231.0 ± 52.4 ms, *p* = 0.09) during atrial fibrillation was not significant.

Using the same group of patients, we then compared the 18 patients (7.2%) with those without a history of VF (Table II). There was no significant difference in the mean age (30.8 ± 13.5 vs 32.2 ± 12.4 years, *p* = 0.7) and sex ratios (men to women: 8 vs 1.9, *p* = 0.06) between the patients with and without VF.

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TABLE I Patients with Multiple Accessory Pathways Compared to Patients with Single Pathways

	No. of Pts.	MAP	No. of Pts.	SAP	OR (CI)	p Value
Age (yr)	31	25.2 ± 10.7	220	33.0 ± 12.4	0.94 (0.90–0.98)	0.001
M:F ratio	31	2.9:1	220	2.0:1	0.68 (0.29–1.6)	0.4
AF	31	16 (52%)	220	64 (29%)	2.59 (1.21–5.54)	0.01
VF	31	5 (16%)	220	13 (6%)	3.06 (1.01–9.27)	0.04
SRR (ms)	31	214.3 ± 48.3	219	231.0 ± 52.4	0.93 (0.86–1.01)*	0.09
ARR (ms)	26	319.1 ± 59.6	204	349.2 ± 72.2	0.99 (0.98–1.00)*	0.04
AP ERP	23	256.1 ± 38.1	190	273.8 ± 28.2	0.98 (0.97–0.99)	0.007
Px RT	31	14 (45%)	220	44 (20%)	3.28 (1.50–7.16)	0.003

* Estimated in 10-ms increments.

AF = atrial fibrillation; AP ERP = accessory pathway anterograde effective refractory period; ARR = average RR interval between 2 preexcited beats during atrial fibrillation; M:F = males:females; MAP = multiple accessory pathways; OR (CI) = odds ratio (95% confidence intervals); Px RT = preexcited tachycardia; SAP = single accessory pathways; SRR = shortest RR interval between 2 preexcited beats during atrial fibrillation; VF = ventricular fibrillation.

TABLE II Patients With Compared to Those Without Ventricular Fibrillation

	No. of Pts.	VF	No. of Pts.	No VF	OR (CI)	p Value
Age (yr)	18	30.8 ± 13.5	233	32.2 ± 12.4	0.99 (0.95–1.03)	0.7
M:F ratio	18	8:1	233	1.9:1	0.24 (0.05–1.06)	0.06
SRR (ms)	17	195.3 ± 48.3	233	231.4 ± 51.6	0.82 (0.71–0.94)*	0.006
ARR (ms)	13	288.5 ± 75.5	217	349.1 ± 69.8	0.98 (0.97–0.99)*	0.003
AP ERP	13	253.8 ± 40.9	200	273.1 ± 28.7	0.98 (0.96–0.99)	0.02
MAP	18	5 (28%)	233	26 (11%)	3.06 (1.01–9.28)	0.04

* Estimated in 10-ms increments.

Abbreviations as in Table I.

Most of the patients had no underlying heart disease. One patient had tachycardia-associated cardiomyopathy, which normalized after surgical ablation of the accessory pathway. The shortest RR (195.3 ± 48.3 vs 231.4 ± 51.6 ms, $p = 0.006$) and average RR intervals (288.5 ± 75.5 vs 349.1 ± 69.8 ms, $p = 0.003$) during atrial fibrillation and anterograde effective refractory period of the accessory pathway (253.8 ± 40.9 vs 273.1 ± 28.7 ms, $p = 0.02$) were shorter in patients with VF. The shortest RR interval during atrial fibrillation ranged from 135 to 500 ms. For every 10-ms decrease in the shortest RR interval, there was an estimated 18% increase in the odds of having VF (odds ratio 0.82, confidence intervals 0.71 to 0.94). The percentage of multiple accessory pathways (27.8 vs 11.2%, $p = 0.04$) in the VF group was significantly higher. Using multivariate stepwise logistic regression analysis, the shortest RR interval during atrial fibril-

lation was the only independent risk factor with a p value <0.05 associated with VF. However, the presence of multiple accessory pathways was associated with a threefold increase in risk for VF, and this magnitude of risk for VF was only minimally altered after adjusting for the shortest RR interval (unadjusted odds ratio 3.1; adjusted odds ratio 2.6, $p = 0.1$).

There were 165 patients with a shortest RR interval <250 ms. When only the criterion of a shortest RR interval <250 ms was used, the sensitivity for detecting VF was 88%, but the positive predictive value was only 9%. The negative predictive value was 98%. However, in patients with multiple accessory pathways and a shortest RR interval <250 ms, the sensitivity was lowered but the positive predictive value was increased to 22% (Table III).

Sudden death is an infrequent but catastrophic complication of the WPW syndrome. The mechanism in the absence of organic heart disease is usually VF after atrial fibrillation with a rapid response over the accessory pathway.^{1–3} Patients resuscitated from VF invariably have inducible atrial fibrillation with a rapid ventricular response and a shortest RR interval between preexcited beats during atrial fibrillation of <250 ms.¹ Attempts at using this criterion prospectively for prognostication are limited by the fact that it has a low positive predictive value⁴ and can be observed in approximately 17% of

TABLE III Predictive Accuracy for Sudden Death

	SRR <250 ms (%)	MAP (%)	SRR <250 ms & MAP (%)
Sensitivity	88	29	29
Specificity	36	89	92
PPV	9	16	22
NPV	98	95	95

NPV = negative predictive value; PPV = positive predictive value; other abbreviations as in Table I.

asymptomatic¹⁰ and up to 50% of symptomatic patients¹¹ with WPW syndrome; thus, the criterion lacks specificity. Previous studies have suggested that patients sustaining VF have a higher incidence of multiple accessory pathways^{1,5} than those with more benign presentations. The one study⁶ failing to find this relation demanded electrocardiographic documentation of the transition of atrial fibrillation to VF in their analysis, a factor that may have underestimated the true incidence of this complication.

The present study supports the view that patients with multiple accessory pathways are more likely to present with both atrial fibrillation and VF. Although the most significant factor distinguishing the patients with and without VF was the presence of a short minimum RR interval, the presence of multiple accessory pathways was associated with 3.1 times odds ratio for developing VF, and this did not change appreciably (2.6 times) when corrected for the shortest RR interval during atrial fibrillation. The small number of patients probably accounted for the lack of a significant p value with multiple regression analysis. The presence of multiple pathways was also shown to increase the positive predictive value of the shortest RR interval <250 ms for VF by 2.4 times, without reducing the specificity. The general uniformity of observations in published reports from different databases^{1,5} supports the view that the presence of multiple accessory pathways confers additional risk of VF.

The reason for the increased prevalence of atrial fibrillation and VF in patients with multiple accessory pathways is not clear. The presence of multiple accessory pathways provides the potential for complex reentrant circuits, which may result in multiple atrial wave fronts during reciprocating tachycardia and thus a greater potential for atrial fibrillation. During atrial fibrillation, rapid activation of the ventricles at multiple sites also

provides a theoretical framework for desynchronization and a greater probability for VF. Finally, the presence of >1 accessory pathway may simply increase the probability that one of these will have a short refractory period.

Regardless of the mechanisms involved, these data suggest that patients with multiple accessory pathways and a shortest RR interval <250 ms are at increased risk for VF. This may be useful when considering nonpharmacologic therapies in the WPW syndrome.

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Percutaneous Balloon Mitral Valvuloplasty in Juvenile Rheumatic Mitral Stenosis

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We report here results and follow-up data of 34 patients <20 years old with rheumatic mitral stenosis (MS) (juvenile MS),¹ who underwent percutaneous balloon mitral valvuloplasty at our medical center.

The patients included 20 girls and 14 boys aged 16 ± 2 years (range 10 to 19) who had severe rheumatic MS with significant pulmonary artery hypertension and severe pulmonary venous hypertension, with no clinical, radiologic or echocardiographic evidence of mitral valve regurgitation, calcification or left atrial thrombus. Associated tricuspid regurgitation and mild aortic regurgitation were present in 4 patients each (15%). Thirty patients (88%) were in New York Heart Association class III to IV and 4 (12%) were in class II. Mitral valve dilatation was performed by the technique described by Lock et al,² with the modification that the J-looped tip of the guidewire was kept in the left ventricular apex instead of in the aorta during balloon dilatation. Procedure failure due to problems related to transseptal puncture occurred in 6 patients. These included atrial injury with hemopericardium (2 patients), severe hypotension and bradycardia (2 patients), inability to cross the atrial septum after the needle puncture (due to either a thickened septum or puncture at an area other than the fossa ovalis [2 patients]).

In 2 patients, the mitral valve was crossed by the Swan-Ganz catheter, but the balloon dilatation catheter could not be negotiated across the mitral valve because of a very narrow opening; at surgery, both patients had pinpoint mitral orifices. In the 26 patients who underwent a successful valvuloplasty, body surface area ranged from 0.90 to 1.65 m², with a mean body surface area of 1.3 ± 0.2 m². A single-balloon technique was used in 20 patients (balloon size, ≤ 23 mm for body surface area <1.2 m², 25 mm for body surface area ≥ 1.2 m²). A double-balloon technique was used in 6 patients. In the latter, the size of the 2 balloons was chosen according to the body surface area; for a body surface area of 1 to 1.25 m², 2 bal-

loons, 15 mm in size, were used; for a body surface area of 1.25 to 1.5 m², 15- and 18-mm sized balloons were used; and for a body surface area of ≥ 1.5 m², 2 balloons, 18 mm in size, were used. Balloon valvuloplasty resulted in a significant decrease in the transmitral end-diastolic pressure gradient (Figure 1), from 23 ± 6 to 8 ± 6 mm Hg ($p < 0.01$), and in a significant increase in mitral valve area, from 0.65 ± 0.25 to 1.8 ± 0.9 cm² ($p < 0.01$). Mean pulmonary artery pressure decreased (Figure 2) from 44 ± 15 to 34 ± 16 mm Hg ($p < 0.02$). The complications encountered were severe mitral regurgitation in 1 patient (due to rupture of the minor chordae of the mitral valve) and cardiac tamponade in another. There were, however, no deaths, and both complications occurred during the learning curve of the technique. Angiographic left-to-right shunt was demonstrated immediately after mitral valve dilatation in 15 of 26 patients, and oximetry evidence of shunt was seen in 6 of 26 patients (23%). On follow-up, 4 of 26 patients had evidence of a left-to-right shunt (15%), with a mean Q_p/Q_s of 2:1. Sixteen patients were studied by cardiac catheterization within 2 weeks and all showed evidence of sustained hemodynamic benefit. All patients reported improvement in symptoms, with a change from New York Heart Association class III to IV to class I to II. Repeat hemodynamic measurements in 10 patients at 3 to 6 months revealed no change in the transmitral end-diastolic gradient (8 ± 3 vs 8 ± 6 mm Hg, immediately after valvuloplasty; difference not significant; Figure 1), a nonsignificant reduction in mitral valve area (1.45 ± 0.6 vs 1.8 ± 0.9 cm²; difference not significant) and a further decrease in mean pulmonary artery pressure that did not reach statistical significance (26 ± 7 vs 34 ± 16 mm Hg; difference not significant; Figure 2). Restenosis (mitral valve area <1.0 cm²) occurred in 2 patients.

Rheumatic MS in India frequently affects children and young adults <20 years old (juvenile MS).¹ Although balloon mitral valvuloplasty has been shown to be an attractive alternative to surgical commissurotomy in adults,^{2,3} reports of this technique in the younger age group are scarce.⁴ In our study (in which three-fourths of patients underwent valvuloplasty with a single-balloon

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FIGURE 1. Graph depicting transmitral end-diastolic gradient before, immediately after balloon dilatation, and at follow-up.

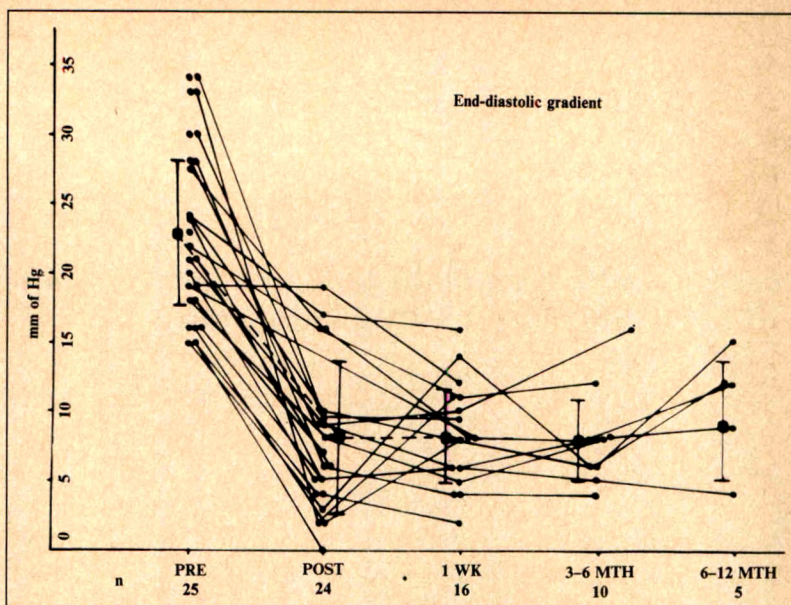
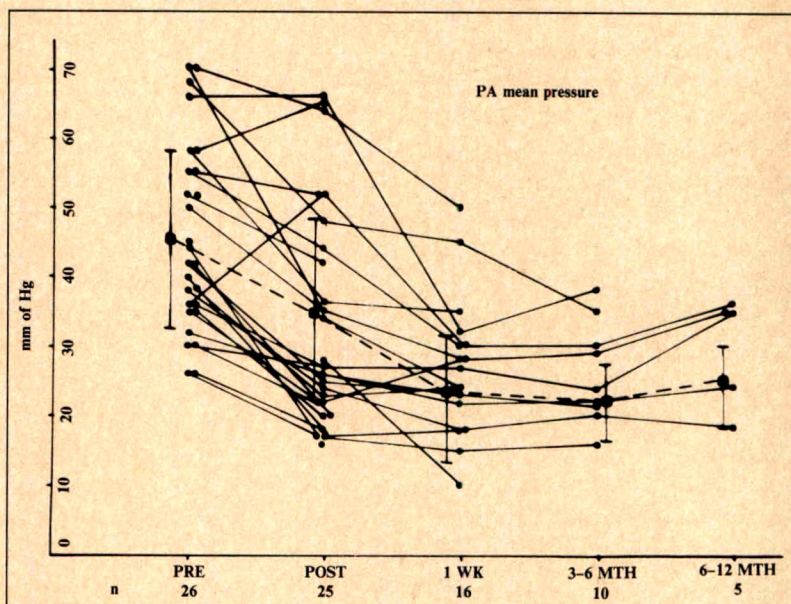


FIGURE 2. Graph depicting mean pulmonary artery pressure before, immediately after balloon dilatation, and at follow-up.



technique), gratifying results were obtained, with an achieved mean mitral valve area of 1.8 cm^2 . The 15% incidence of atrial septal defect and the 3.8% incidence of severe mitral regurgitation in this series of young patients are no different from figures available from studies in older patients.⁵ However, we had a higher failure rate in our group of patients. Some of the difficulties related to the transseptal puncture could have been avoided by 2-dimensional echocardiographic guidance at the time of the puncture. In patients with very narrow mitral orifices, sequential dilatations, with use of smaller sized catheters, initially followed by larger sized catheters, may help to avoid failures. Follow-up studies have shown sustained hemodynamic improvement in most patients. These pre-

liminary data suggest that even a single-balloon technique is effective in producing adequate relief of MS in younger patients. Although mitral restenosis in 2 of 10 patients restudied at an interval of 6 months appears to be a rather high figure, a longer follow-up of a larger number of patients is required to determine the true incidence of restenosis in juvenile MS subjected to balloon valvuloplasty.

Acknowledgment: We are indebted to P. Venugopal, MS, MCh, MD, Chief of Cardiovascular and Thoracic Surgery, and his colleagues for surgical back-up.

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Reversal of Changes in Left Ventricular Diastolic Filling Associated with Normal Aging Using Diltiazem

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Congestive heart failure is a common problem in clinical geriatrics and often the result of diastolic rather than systolic dysfunction.¹ Normal aging is associated with a reduction in the rate of calcium ion uptake by the sarcoplasmic reticulum.² Because intracellular handling of calcium may affect isovolumic relaxation and left ventricular (LV) compliance, a calcium antagonist may be beneficial. The pattern of LV diastolic filling may be accurately characterized by both pulsed Doppler transmitral flow velocities³ and radionuclide scintigraphy.⁴ The present study tests the hypothesis that a calcium antagonist, diltiazem, may be effective in reversing the impairment of early diastolic LV filling seen in elderly subjects.

The subjects consisted of 2 groups, each given a single 90-mg oral dose of diltiazem. They included 10 healthy young adults (6 men and 4 women, mean age \pm standard deviation 29 ± 1 years) and 11 healthy elderly subjects (7 men and 4 women, aged 68 ± 3 years). All subjects were free of cardiovascular and renal disease by history and physical examination and none had a history of cigarette smoking or was taking any medication. Complete blood count, serum electrolytes, blood urea nitrogen, creatinine, fasting glucose, resting electrocardiogram, and results of maximal exercise treadmill tests were all normal. No caffeine or alcohol-containing foods or beverages were allowed

for at least 12 hours before the study. Informed consent was obtained from all subjects.

Two-dimensionally guided M-mode and transmitral pulsed Doppler measurements were performed using an HP77020A (Hewlett-Packard Co., Andover, Massachusetts) echocardiograph and 2.5-MHz transducer at baseline and 3 hours after administration of diltiazem. M-mode recordings were obtained according to the recommendations of the American Society of Echocardiography.⁵ Simultaneous phonocardiography and M-mode recordings were used to assess the interval from the aortic component of the second heart sound to mitral valve opening. The value was rate-corrected to estimate isovolumic relaxation time.⁶ Pulsed Doppler transmitral velocities were taken from the apical 4-chamber view between the tips of the mitral leaflets³ by the same operator. Doppler data were manually traced and digitized. Peak velocities of the early and atrial filling waves were determined with velocity-time integrals of the early and atrial filling waves obtained by integrating flow velocity profiles at 4-ms intervals. Percent early filling was assessed by dividing the area under the early wave by the total velocity-time integral. Percent filling during the first one-third of diastole was calculated as the percent of the velocity-time integral during the first third of diastole. Time for 50% filling was calculated as the time to attain 50% of the total velocity-time integral. Three to 5 successive Doppler spectra were analyzed in a blinded fashion.

Radionuclide scintigraphy was performed in 4 young and 11 older subjects at baseline and 90 minutes after diltiazem using the in-vitro technique.⁷ LV filling fractions were calculated using the LV volume-time curve. Filling fractions were calculated by dividing the number of frames from end-diastole to the end of the volume curve by 3.

All results are expressed as mean \pm standard deviation. Comparisons between groups were made using the Student's unpaired *t* test. Data analysis before and

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TABLE I Doppler Data Before and After Diltiazem in Young Adult and Elderly Groups

	Young Adult (n = 10)		Healthy Elderly (n = 11)	
	Baseline	After Diltiazem	Baseline	After Diltiazem
Heart rate (beats/min)	57 ± 10	58 ± 8	56 ± 7	53 ± 8
Systolic blood pressure (mm Hg)	107 ± 6	108 ± 5	139 ± 8*	129 ± 12†
Isovolumic relaxation time (s)	0.073 ± 0.013	0.078 ± 0.011	0.102 ± 0.024*	0.08 ± 0.037†
Peak E-wave velocity (m/s)	0.64 ± 0.11	0.66 ± 0.07	0.49 ± 0.13‡	0.53 ± 0.10§
Peak A-wave velocity (m/s)	0.34 ± 0.06	0.37 ± 0.05	0.60 ± 0.14‡	0.57 ± 0.15
Peak E/peak A velocity	1.9 ± 0.4	1.8 ± 0.2	0.8 ± 0.2‡	1.0 ± 0.2§
% E-wave filling	79 ± 5	77 ± 3	60 ± 9‡	64 ± 7
Time for 50% LV filling (ms)	144 ± 19	147 ± 24	266 ± 85‡	232 ± 79
% Filling first third of diastole	61 ± 6	61 ± 4	45 ± 8‡	50 ± 8§

* p < 0.02 vs baseline young adult.

† p < 0.08 vs baseline healthy elderly.

‡ p < 0.05 vs baseline young adult.

§ p < 0.05 vs baseline healthy elderly.

after diltiazem were made using the Student's paired *t* test. A *p* value < 0.05 was considered significant. Bonferroni correction was applied to minimize the possibility of a chance significance.

No patient had an adverse reaction to diltiazem. At baseline, the isovolumic relaxation time was significantly increased (Table I) in the healthy old subjects compared with young adults. In young adult subjects, there was no change after administration of diltiazem, although in the elderly, there was a trend toward shortening of relaxation time. There were significant differences between the young adult and elderly in peak early/peak atrial velocity, percent early filling, time for 50% filling, percent filling in the first third of diastole, and peak early/peak atrial velocity

at baseline (Table I). After diltiazem, there were no changes in any of the Doppler parameters in young adults. In the healthy elderly (Figure 1, Table I), however, there were significant increases in peak early velocity, percent filling during the first one-third of diastole and peak early/peak atrial velocity. Radionuclide scintigraphy documented a significant increase in the first third filling fraction (Table II) in the healthy elderly. No change was noted in the healthy young adults.

The results of this study demonstrate that there are significant differences between healthy young adults and healthy elderly in resting isovolumic relaxation time, as well as transmitral pulsed Doppler and radionuclide indexes of LV filling. Isovolumic relaxation time was prolonged in the elderly, and shortened with diltiazem. The Doppler and radionuclide data demonstrate an age-related shift in diastolic filling toward the end of diastole. These changes are partially reversed with a calcium antagonist.

With healthy aging, LV systolic function remains intact,¹ but there is an impairment of early diastolic filling, with the atrial contribution becoming increasingly prominent.⁸ These changes occur in the absence of clinically evident myocardial ischemia or arterial hypertension and appear to be independent of the age-related increase in LV mass. This recognition of impaired diastolic function with advancing age and clinical congestive heart failure with preserved systolic function has stimu-

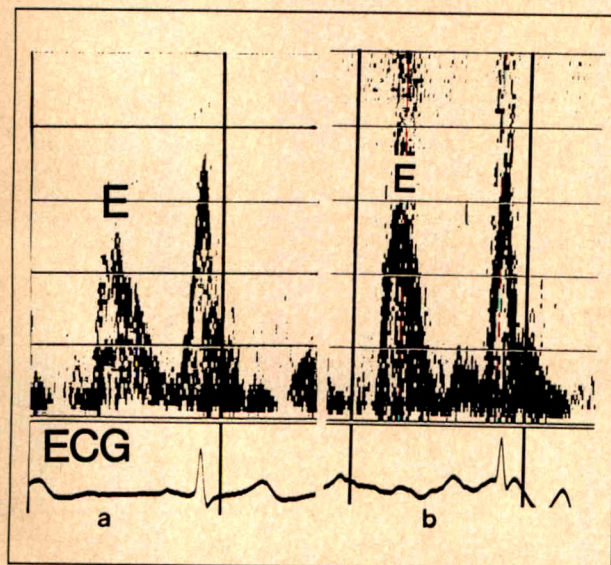


FIGURE 1. Transmitral Doppler spectra from an individual patient before (a) and after (b) ingestion of 90 mg of diltiazem. Each bar represents 0.2 m/s. After ingestion of the calcium blocker, there is an increase in peak early (E) velocity with an increase in peak early/peak atrial velocity. ECG = electrocardiogram.

TABLE II Radionuclide Filling Data in the Healthy Elderly Before (Baseline) and After Diltiazem

	Baseline	After Diltiazem
First third filling fraction	0.42 ± 0.15	0.51 ± 0.11*
Second third filling fraction	0.30 ± 0.14	0.21 ± 0.08*
Third third filling fraction	0.28 ± 0.07	0.28 ± 0.07

* p < 0.05 vs baseline.

lated interest in the identification of therapies to improve diastolic performance. Our study confirms the work of others, that normal aging is associated with a prolongation of isovolumic relaxation time and impairment of early diastolic LV filling.⁹ There is a decrease in the peak early wave velocity with a concomitant increase in the peak atrial wave velocity and prolongation of time for 50% LV filling. Correspondingly, the percent filling during the first third of diastole and percent early wave filling decline with age.

The current study demonstrates that with calcium blocker ingestion, there is an improvement in diastolic filling indexes in the healthy elderly, with no change in the young adults. This suggests that LV relaxation may already be optimal in the healthy young group, or that further enhancement of diastolic filling cannot be mediated by drugs that inhibit calcium entry. Diltiazem and other calcium antagonists have been shown to improve Doppler indexes of LV filling in the setting of coronary ischemia.¹⁰ We specifically excluded subjects with a history of coronary artery disease, smoking, diabetes or systolic dysfunction. Furthermore, all the elderly subjects in the study underwent maximal exercise testing without signs of myocardial ischemia. Therefore, the demonstrated improvements after administration of calcium blockers were likely not due to amelioration of myocardial ischemia, but rather to a partial reversal of calcium-mediated age-related myocardial changes.

The Doppler data offer an indirect assessment of LV diastolic performance. The flow velocity wave forms may be influenced by heart rate and loading conditions.¹¹ In this study, heart rate did not change. The relative contribution of the reduction in blood pressure to the observed change in diastolic indexes cannot be precisely delineated. A decrease in preload, as with nitroglycerin, has been shown to decrease peak early wave velocity.^{11,12} Strictly speaking, improved LV compliance after calcium blocker ingestion cannot be definitively proven from our study. However, we have shown that isovolumic relaxation time is reduced. At similar heart rates a decrease in relaxation time would lead to a shortening of the time for left atrial filling and thus a decrease in peak early velocity. Thus, it is likely that the improvement in diastolic filling indexes is at least partially attributable to improved LV diastolic performance. We examined relatively acute effects. Additional studies are needed to assess

the effects of chronic calcium blocker therapy and to determine if an acute challenge can predict long-term clinical improvement.

In this study, we have demonstrated distinct differences in relaxation time and both Doppler and radionuclide indexes of LV filling between young adults and healthy elderly. After administration of diltiazem, there were improvements in noninvasive indexes of LV filling in the elderly group, with no change in the young adult group. These changes, if sustained, suggest that calcium antagonists may help reverse the abnormal pattern of LV filling in the elderly and prove useful for elderly patients with diastolic dysfunction.

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Spontaneous Regression of Cardiac Rhabdomyoma

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Multiple cardiac rhabdomyomas in a neonate with tuberous sclerosis were first described by Von Recklinghausen in 1862. These hamartomas are the cardiac tumors most frequently encountered during infancy and childhood. Rhabdomyomas account for 45% of primary heart tumors in children and represent 53% of primary benign childhood cardiac tumors.¹ Approximately 30% of patients with tuberous sclerosis have cardiac rhabdomyomas.² Their natural history is unclear because most reviews on this subject are based on autopsy data. The prognosis for cardiac rhabdomyomas is believed to be grim because of reported fatality rates of 53% by the first week of life and 78% by 1 year of age.^{2,3} With widespread use of echocardiography in pediatrics during the last 2 decades, it has become clear that rhabdomyomas result in a wide spectrum of clinical manifestations, ranging from a total absence of symptoms to intrauterine or sudden postnatal death. Also reported are hydrops fetalis, dysrhythmias, inflow or outflow obstruction, congestive heart failure and possibly cerebral embolization. Histologic examination of these masses in 1923 was suggestive of spontaneous regression.⁴ Isolated clinical reports of spontaneous regression have recently appeared.⁵ We now describe a series of 5 infants with tuberous sclerosis who had close documentation of the size of their 13 tumors.

Between 1973 and 1989, 25 patients were diagnosed with cardiac rhabdomyomas. At the time of the initial diagnosis, 10 patients were aged <4 weeks, 8 were >1 and <12 months, and 1 was >12 months. Five infants underwent operation, with 1 death, and 4 of these patients have been reported on previously.⁶ One patient with diffuse rhabdomyomatosis was initially diagnosed at 1 day of age, was thought to be inoperable and died of intractable ventricular tachycardia at 6 months of age. Five patients with tuberous sclerosis and cardiac rhabdomyoma had a single echocardiographic study and their outcome is unclear. Four patients have been followed elsewhere and available reports indicate spontaneous regression of the tumors, but we excluded them from the present

study because of lack of serial measurements of the tumors. The remaining 5 infants with tuberous sclerosis and rhabdomyomas had serial measurements of the masses performed during follow-up studies and form the basis of this report. The nature of the masses was assumed to be rhabdomyoma because of the diagnosis of tuberous sclerosis; histologic confirmation was not obtained. All patients underwent complete cardiologic and neurologic evaluation. Serial electrocardiograms and echocardiograms were obtained for all patients. Cardiac catheterization and cineangiography were performed in 2 patients. The location, number and size of each tumor was determined. Electronic calipers were used to measure the circumference of each mass in ≥ 2 planes. An average of these measurements was used to follow the changes in the size of each tumor. Linear regression analysis was performed on each tumor circumference with respect to patient age over time. Three serial measurements were used for analysis of 7 tumors. The remaining 6 had resolved at the time of the second follow-up study.

Three of the 5 patients were white and 3 were girls. The ages at initial presentation were 21, 1, 5, 6 and 300 days, respectively (Table I). The first patient presented with supraventricular tachycardia and Wolff-Parkinson-White syndrome; the remaining 4 patients had asymptomatic heart murmurs. All patients developed cutaneous, neurologic and radiologic abnormalities of tuberous sclerosis. Family history was positive for tuberous sclerosis in 1 patient.

The cardiothoracic ratio on chest x-ray was increased in patients 2 and 5. The electrocardiogram revealed right ventricular hypertrophy in patients 2 and 5 and right atrial enlargement in patients 3 and 5. The diagnosis of cardiac tumor was made by echocardiography in all patients. Cardiac catheterization and cineangiography were performed in patients 1 and 2. Magnetic resonance imaging was obtained in patient 5.

Tumor sites are listed in Table I. Of these, 12 were ventricular (8 right, 4 left) and 1 was right atrial. There were 10 intracavitary and 3 intramural masses. A solitary mass was seen in 2 and multiple tumors were present in 3 patients. There was a 5-mm Hg gradient recorded across the right ventricular outflow

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TABLE I Tumor Regression Characteristics

Pt. No.	Age (days)	Sex	Tumor Site	Circumference			Regression Coefficient*	Rate of Tumor Regression (mm/month)	Age at Resolution (yr)
				Initial	Maximal	Final			
1	21	M	RV cavity	2.3	2.3	0			0.6
2	1	F	RV cavity	8.8	10.3	0	-0.93 [†]	2.1	3.5
			RV mural	10.8	10.8	4.1 [§]	-0.99 [†]	1.5	
3	5	F	RA cavity	6.5	8.4	6.9	-0.15	0	
			RV cavity	2.1	2.1	0			0.4
			RV cavity	2.6	2.6	0			0.4
			RV cavity	2.8	2.8	0	-0.99 [†]	0.9	2.5
			RV mural	3.0	3.0	0			0.4
			LV cavity	2.1	2.1	0			0.4
4	6	F	LV cavity	2.8	3.1	0	-0.92 [†]	0.9	3.5
			LV cavity	3.3	3.9	0	-0.89 [†]	2.3	1.2
			LV mural	0.5	0.5	0			0.3
			RV cavity	6.5	6.8	2.6	-0.96 [†]	6.0	

* For the regression of tumor size over time.

[†] $p < 0.01$; [‡] $p < 0.05$.

[§] Includes papillary muscle.

LV = left ventricular; RV = right ventricular.

tract in patient 1 (catheterization), a 4 mm-Hg gradient across the tricuspid valve in patient 2 (catheterization), no gradients in patient 3 (Doppler), a 15-mm Hg mean gradient across the left ventricular outflow tract in patient 4 (Doppler), and a 65-mm Hg peak gradient across the right ventricular outflow tract in patient 5 (Doppler). The circumference of the tumors ranged between 0.5 and 10.8 cm.

All patients remained asymptomatic during the follow-up period of 12.5, 7.0, 4.5, 3.5 and 0.6 years, respectively. The site, initial circumference, final circumference, rate of tumor regression and age at com-

plete resolution of the tumor are listed in Table I. There was a transient increase in the circumference of 4 tumors (10, 17, 18 and 30%) followed by rapid resolution. The rate of regression ranged between 0.9 and 6.0 mm/month. The regression coefficients of ventricular tumor size over time range between -0.89 and -0.99. The right atrial tumor showed no change in size. Figures 1 to 3 are examples of spontaneous regression of rhabdomyomas. An example of a regression curve with 8 data points is shown in Figure 4.

We reviewed data reported in 25 patients with ventricular rhabdomyomas thought to have shown spontaneous regression between 1975 and 1990.^{5,7,8} The regression of 13 tumors occurred between 0.4 and 6.0 years of age (median 1.0). Spontaneous regression of atrial rhabdomyoma has been reported in 2 patients.^{9,10} The value of surgical resection of symptomatic tumors is well estab-

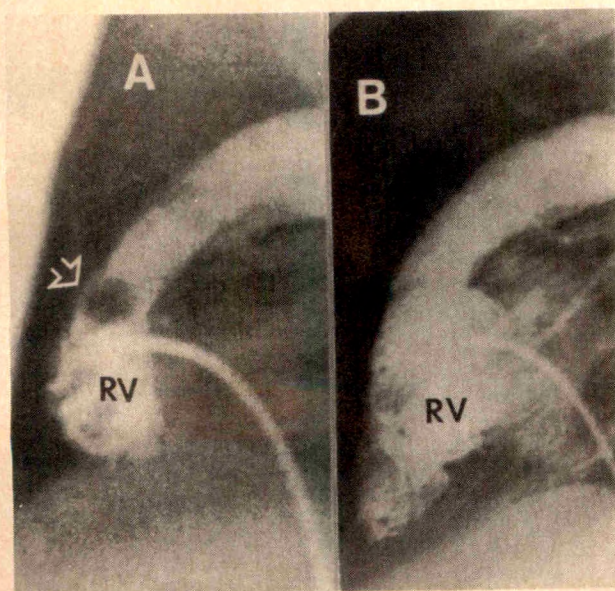


FIGURE 1. Right ventricular cineangiogram of patient 1. (A) Arrow indicates the filling defect in the right ventricular outflow tract, seen at 4 weeks of age. (B) Follow-up study at 7 years of age reveals complete resolution. RV = right ventricle.

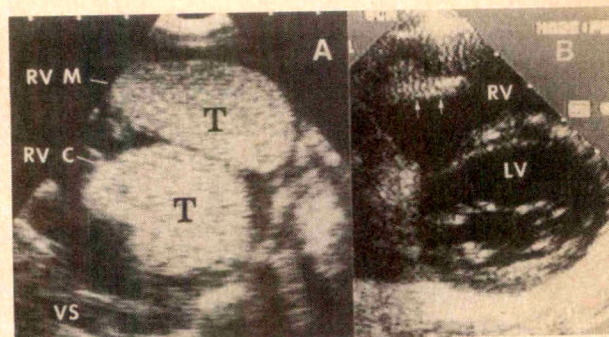


FIGURE 2. Two-dimensional echocardiogram of patient 2. (A) Modified short-axis view of the right ventricular cavity (RV C) obtained at 1 day of age reveals a large cavity as well as a well-circumscribed intramural mass. (B) Follow-up study at 3.5 years of age reveals complete resolution of masses and only an echodense area (white arrows) of the papillary muscle remains. LV = left ventricle; RV = right ventricle; RVM = right ventricular mural; T = tumor; VS = ventricular septum.

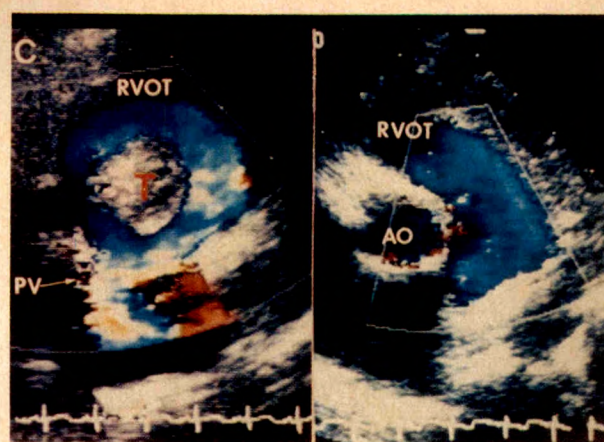
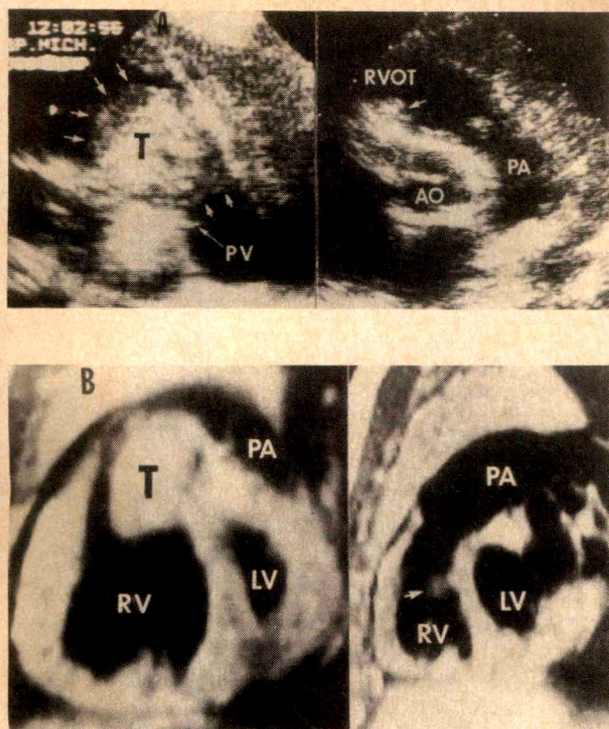


FIGURE 3. Patient 5. (A) Short-axis high parasternal view obtained at 10 months of age (left) reveals a large rounded mass almost completely occluding the right ventricular outflow tract (RVOT) (arrows). The outer shell of the mass appears nonhomogeneous and less echodense than its central portion. A follow-up study at 17 months of age (right) reveals almost complete resolution of the mass. (B) Magnetic resonance imaging at 12 months of age (left) reveals a large mass in the right ventricular outflow tract. A follow-up study at 18 months of age (right) reveals a minimal residual mass (arrow). (C) Color-flow Doppler study at 10 months of age (left) reveals the bifid pattern of flow around the mass in the right ventricular outflow tract (RVOT). A follow-up study at 17 months of age (right) shows normal flow pattern in the pulmonary artery (PA). Ao = aorta; LV = left ventricle; PV = pulmonary valve; RV = right ventricle; T = tumor.

lished.^{6,11} Our data showed regression of all 12 ventricular tumors, with complete resolution of 83%. Complete regression of 6 ventricular tumors occurred by 1 year of age and an additional 4 completely resolved between 1.0 and 3.5 years of age. Near complete resolution of 2 ventricular tumors was observed between 2.4 and 3.5 years of age. Transient increase in the circumferences of 4 ventricular tumors was observed before regression. The explanation for this observation remains unclear and cannot be entirely explained by technical difficulties in tracing the outline of tumors. Our data do not support the Konkol et al's recommendation¹² to operate on all cavitary rhabdomyomas in order to prevent central nervous system embolization. Unless critical obstruction or dysrhythmia is present, medical follow-up should be the preferred treatment for cardiac rhabdomyoma.

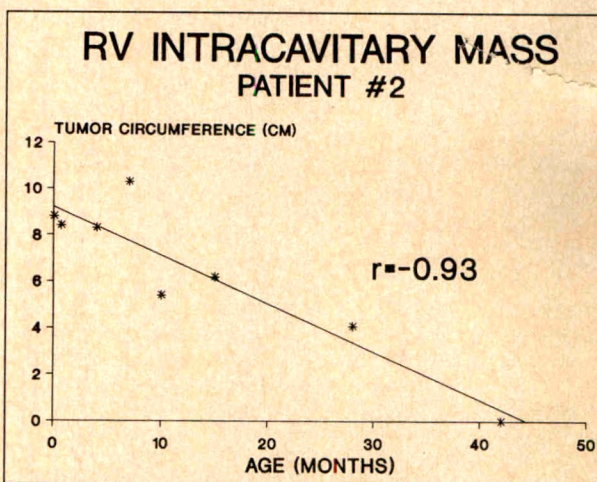


FIGURE 4. Regression curve for a right ventricular (RV) mass in patient 2. The correlation coefficient is -0.93 . * Actual individual measurements on the vertical axis.

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Afterload Dependence of Echocardiographic Left Ventricular Ejection Force Determination

Thomas R. Lloyd, MD, and Richard L. Donnerstein, MD

Isaaz et al¹ have proposed a new echocardiographic index of left ventricular (LV) contractile function based on the force imparted to blood ejected during the accelerative phase of systole, according to Newton's second law. This index correlated with ejection fraction in patients with congestive heart failure¹ and responded appropriately after replacement therapy in patients with hypothyroidism.² Using a mock circulation and clinical example, we have shown that LV ejection force as determined by Isaaz et al¹ is a strongly afterload-dependent index of contractile function.

We simplified calculation of LV ejection force, such that $\text{ejection force} = \rho \cdot \text{CSA} \cdot \frac{1}{2}(\text{Vpk})^2$ (Appendix). The relation between ejection force and afterload was studied in a water-filled Donovan mock circulation with a biventricular assist device (Novacor, Oakland, California) powered by a pneumatic driver (Symbion, Salt Lake City, Utah). Pressure in the model aorta was monitored with a micromanometer-tipped catheter (Millar Instruments, Houston, Texas). Air bubbled into the model right atrium provided ultrasonic contrast. Diastolic blood pressure was systematically varied to alter LV afterload while force was held constant at 1 of 3 values by fixing the pressure applied to the assist device diaphragm at 125, 150 or 175 mm Hg. Heart rate was held constant at 65 min⁻¹. The density of water and the cross-sectional area of the mock aortic root remained constant, so that the calculated ejection force could be changed only by changes in Doppler flow velocity. A pulsed Doppler probe, positioned parallel to flow, was incorporated into the mock aortic root for velocity measurements. The calculated ejection force was related to diastolic pressure and LV applied force by multiple regression analysis. If the calculated ejection force truly represents contractility, it should vary with LV applied force but not with diastolic blood pressure. The calculated ejection force correlated appropriately with LV applied force, but varied inversely with diastolic blood pressure (Figure 1).

We observed a clinical example that confirms the afterload dependence of LV ejection force. A 9-

month-old infant presented in severe congestive heart failure from systemic carnitine deficiency. Ascending aortic size and pulsed Doppler flow velocity were measured from the suprasternal notch during initiation of vasodilator therapy with sodium nitroprusside. Arterial blood pressure (from a femoral artery catheter) was noted during each Doppler recording. Examples are shown in Figure 2. The relation between LV ejection force (by our modification of the Isaaz formula) and diastolic blood pressure is shown in Figure 3. Again, the calculated LV ejection force varied inversely with diastolic blood pressure in this patient, whom we believe had little ability to vary true LV force development.

We have simplified the LV ejection force equation proposed by Isaaz et al¹ so that it requires measurement only of peak aortic Doppler flow velocity and aortic cross-sectional area, eliminating measurement of time to aortic peak velocity, integration of the accelerative phase of the aortic Doppler flow velocity profile, and approximation of the acceleration of aortic blood (both methods assume a standard value for the density of blood). The measurements eliminated are those which in our experience are most difficult to measure accurately and reproducibly.

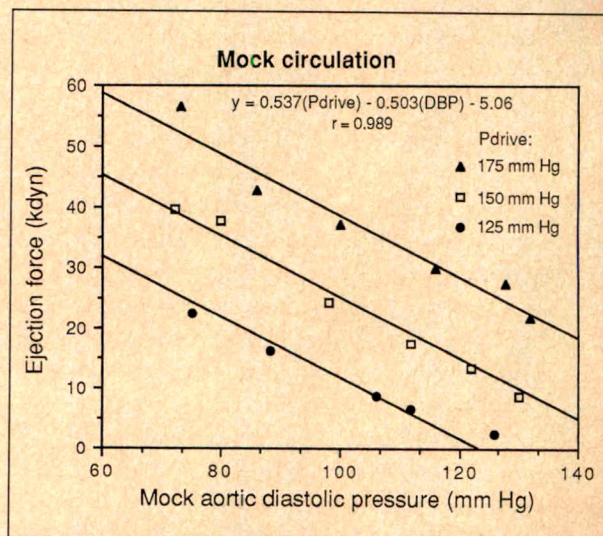


FIGURE 1. Left ventricular ejection force from the mock circulation, calculated by our modification of the method of Isaaz et al,¹ is plotted against diastolic blood pressure (DBP) in the mock aorta. Regression lines from multiple regression analysis indicate the strong statistical relations between ejection force and both driving pressure (Pdrive) applied to the assist device ($p < 0.0001$) and diastolic pressure ($p < 0.0001$).

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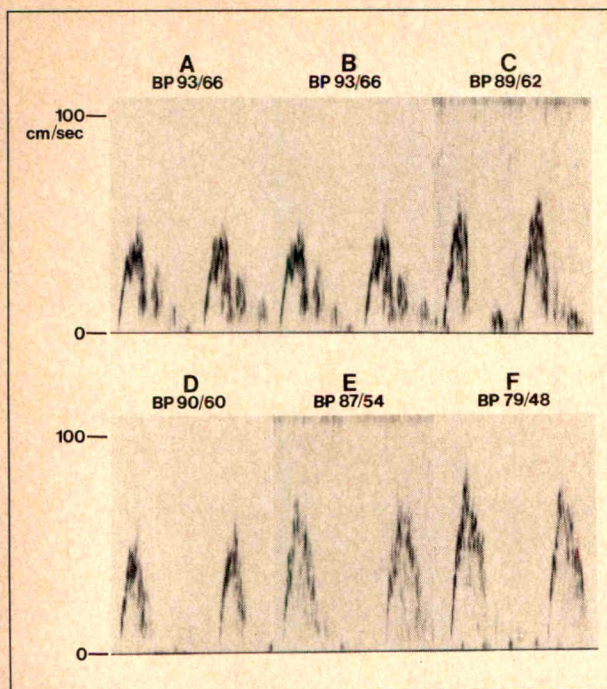


FIGURE 2. Pulsed Doppler tracings from the ascending aorta from a 9-month-old patient with cardiomyopathy during institution of vasodilator therapy with sodium nitroprusside (see text). Systolic and diastolic femoral artery blood pressures (BP) at the time of Doppler recording are indicated in each panel: C, obtained before infusion of nitroprusside; remaining tracings were recorded during infusion of nitroprusside at 0.5 $\mu\text{g/kg/min}$ (A), 1.0 $\mu\text{g/kg/min}$ (B and D), 2.0 $\mu\text{g/kg/min}$ (E), and 3.0 $\mu\text{g/kg/min}$ (F). Note the clear relation between aortic Doppler velocity and diastolic arterial pressure.

We believe that our modification of the formula of Isaaz et al will improve the precision of this measurement.

Aortic peak Doppler flow velocity has been used as an index of LV performance by some investigators,^{3,4} whereas others have used modifications, such as Doppler flow acceleration⁵ or indexing velocity to LV and aortic size.⁶ Aortic peak Doppler flow velocity is the major determinant of the calculated LV ejection force because its value is squared in the computation. The afterload dependence of Doppler velocity is intuitive: When afterload is maximum (aortic occlusion), ejection will cease and peak ejection velocity will be zero. It is therefore not surprising that the ejection force index of Isaaz et al should prove to be afterload-dependent; indeed, the method was validated against ejection fraction,¹ a notoriously load-dependent measure of contractility.

Conceivably, calculated ejection force could be combined with diastolic blood pressure to produce an afterload-independent estimate of LV force development. The product of diastolic pressure and aortic cross-sectional area can be converted to force units (kdyn) and added to the calculated ejection force to yield an estimate of LV developed force. To obtain an afterload-independent estimate from our data, ejection force would have to be

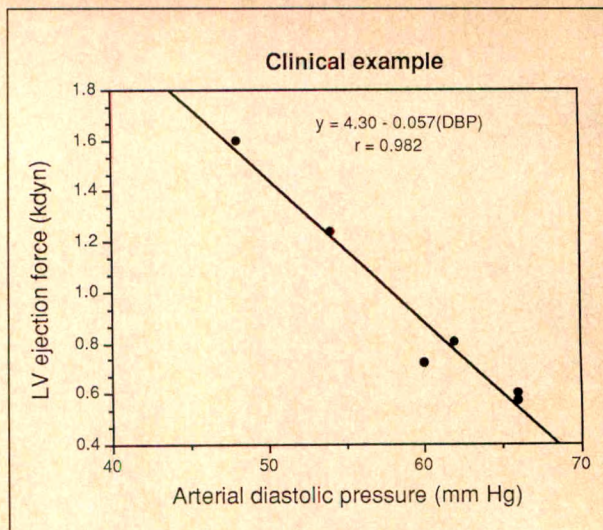


FIGURE 3. Left ventricular ejection force calculated by our modification of the method of Isaaz et al¹ plotted against diastolic blood pressure (DBP) using the data from our patient example. Regression line is shown. Calculated ejection force decreased with increasing diastolic blood pressure ($p < 0.001$).

multiplied by 8.3 in the mock circulation and by 45.5 in our patient example. It should not be surprising that the method of Isaaz et al substantially underestimates ejection force, because it considers acceleration only of the mass of blood actually ejected from the ventricle.¹ With each heart beat, blood is accelerated throughout the arterial tree, and the motive force for this acceleration must come from the left ventricle. It may indeed be possible to develop a formulation that includes all the components of LV developed force, i.e., the forces necessary to overcome diastolic blood pressure and aortic impedance as well as the full accelerative component of ventricular force. However, the current formulation of LV ejection force exhibits such strong afterload dependence that the usefulness of this noninvasive index of ventricular performance is substantially limited.

APPENDIX

By Newton's second law, force = mass \cdot acceleration. As shown in Equation 1, the mass ejected during the accelerative phase of ejection is the product of blood density (ρ), aortic cross-sectional area (CSA), and the time integral of Doppler flow velocity (V) from the instant before ejection begins (time = 0) to the time of peak Doppler velocity (time = t_{pk}), and acceleration is the time derivative of Doppler velocity (dV/dt):

$$\text{Force} = \rho \cdot \text{CSA} \cdot \int_0^{t_{pk}} V \cdot dt \cdot (dV/dt). \quad [1]$$

Isaaz et al¹ approximated acceleration as peak Doppler velocity (V_{pk}) divided by t_{pk}, producing:

$$\text{Force} = \rho \cdot \text{CSA} \cdot \int_0^{t_{pk}} V \cdot dt \cdot V_{pk}/t_{pk}. \quad [2]$$

However, we chose to combine the time integral with the time differential, evaluating the integral over the velocity values from t_0 to tpk , such that:

$$\text{Force} = \rho \cdot \text{CSA} \cdot \int_0^{V_{pk}} V \cdot dV. [3]$$

We then solved the definite integral to produce our simplified expression for ejection force (note that $V_0 = 0$ by definition), so that:

$$\text{Force} = \rho \cdot \text{CSA} \cdot \frac{1}{2}(V_{pk})^2. [4]$$

Acknowledgment: We are grateful to Jack Copeland, MD, for use of the mock circulation and to Marilyn Cleavinger and Farshad Shirazi for technical assistance.

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Unstable Myocardial Ischemia After the Initiation of Niacin Therapy

Richard C. Pasternak, MD, and Benet S. Kolman, MD

Niacin has been used as a pharmacologic agent for the treatment of hypercholesterolemia for >3 decades.¹⁻³ Current interest in niacin therapy has been reawakened, in part as a result of its status as a "first-line" drug in the treatment of hyperlipidemia according to the National Cholesterol Education Program guidelines.⁴ Unfortunately, adverse effects limiting its use are frequent. These include gastrointestinal problems, flushing, atrial arrhythmias, abnormalities of liver function, hyperglycemia and hyperuricemia. We encountered an apparently unrecognized adverse effect of niacin that may be of great clinical importance in patients with active ischemic heart disease—namely, worsening of unstable ischemia, perhaps on the basis of coronary steal.

Case 1: A 65-year-old man was hospitalized for unstable angina. Symptoms were controlled with a medical regimen of isosorbide dinitrate and diltiazem. Cardiac catheterization disclosed normal left ventricular function and a total proximal right coronary artery occlusion with bridging collateral vessels and, distally, a total occlusion of a large posterior interventricular branch of the right coronary artery with well-developed collateral vessels from the left circumflex artery. The left anterior descending artery contained an

80% diameter narrowing and the left circumflex coronary artery had a 60% diameter narrowing.

Because of an extremely unfavorable total cholesterol to high-density lipoprotein cholesterol ratio (12.3:1), he was begun on niacin therapy before hospital discharge. While at bed rest on the day after catheterization, the patient received an initial oral dose of 200 mg of crystalline niacin, in combination with his usual 30 mg of diltiazem (which had never produced adverse effects or hypotension and which he had been receiving 3 times daily). Within 45 minutes (before taking isosorbide dinitrate), he had flushing associated with a decrease in systolic blood pressure from 120 to 90 mm Hg. Shortly thereafter, he had severe substernal chest tightness, requiring sublingual nitroglycerin, and 15 mg of intravenous morphine sulfate for pain control. He developed new anterolateral ST-segment depression and T-wave inver-

sions (Figure 1). These changes persisted for 72 hours, while cardiac enzymes remained normal (peak creatine kinase 88 IU/liter, upper limit of normal 200 IU/liter). After clinical stabilization, both isosorbide dinitrate and diltiazem were resumed without adverse effects and without further ischemic symptoms. No further doses of niacin were given.

Case 2: A 64-year-old man was hospitalized after the recent onset of exertional and rest angina. He was begun on 10 mg of propranolol and 20 mg of nifedipine, each given every 6 hours, and nitropaste, given every 4 hours. With this regimen he was pain-free and hemodynamically stable, without hypotension after doses of these medications. One day later, for treatment of a "high-risk" total cholesterol to high-density lipoprotein cholesterol ratio (6.9:1), crystalline niacin was begun at an initial dose of 100 mg, in combination with the previously well-tolerated nifedipine and propranolol doses. Thirty to 45 minutes after the first dose of niacin, while lying in bed, the patient complained of being hot and was found to be intensely diaphoretic

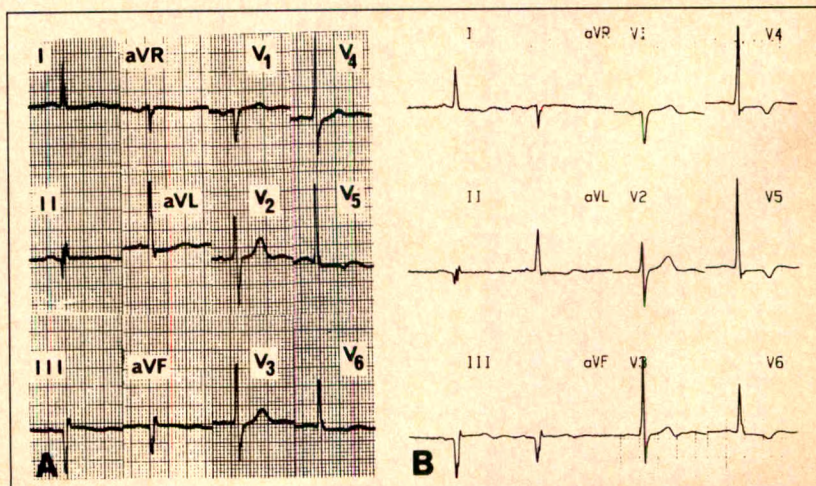


FIGURE 1. A, baseline electrocardiogram from case 1. There are old inferior Q waves and diffuse ST-T wave abnormalities. B, electrocardiogram obtained at time of acute ischemic episode (3 days after A) showing new ST-T changes (compared with baseline tracing); most marked are the new or deeper T-wave abnormalities in leads V4 to V6.

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and flushed. His systolic blood pressure decreased to 60 mm Hg. He was placed in the Trendelenburg position and given intravenous fluids. Five minutes later he complained of severe substernal pressure. His systolic blood pressure had increased to 90 mm Hg. Severe chest discomfort persisted for 3 hours, requiring intravenous nitroglycerin for relief. The electrocardiogram revealed new ST-segment elevation inferiorly (Figure 2A). New Q waves developed in these leads (Figure 2B), and total creatine kinase rose from 50 to 475 IU/liter (creatinine kinase MB fraction from 0 to 4%). He was thought to have sustained a small acute inferior myocardial infarction. No further symptoms occurred when his antiischemic regimen was resumed (niacin was discontinued). He was discharged 8 days after this acute event.

Coronary angiography on a later admission revealed 3-vessel coronary artery disease (95% diameter narrowing of the mid-right, 95% diameter narrowing of the mid-left circumflex and 60 to 70% diameter narrowing of the left anterior descending coronary arteries) with collateral vessels to the distal right coronary artery.

Prescribed to stable outpatients, niacin is extremely safe.^{2,3} However, in patients with unstable ischemic syndromes, niacin, particularly when given with other vasoactive drugs, can possibly produce a complication, the exacerbation of myocardial ischemia, that has not been previously described. The temporal relation between the administration of niacin and the problems noted in the aforementioned patients makes it highly likely that niacin played an important role in precipitating their further ischemia.

Niacin has well-known vasodilating properties,⁵ although the particular vascular bed or type of resistance vessel affected has not been well

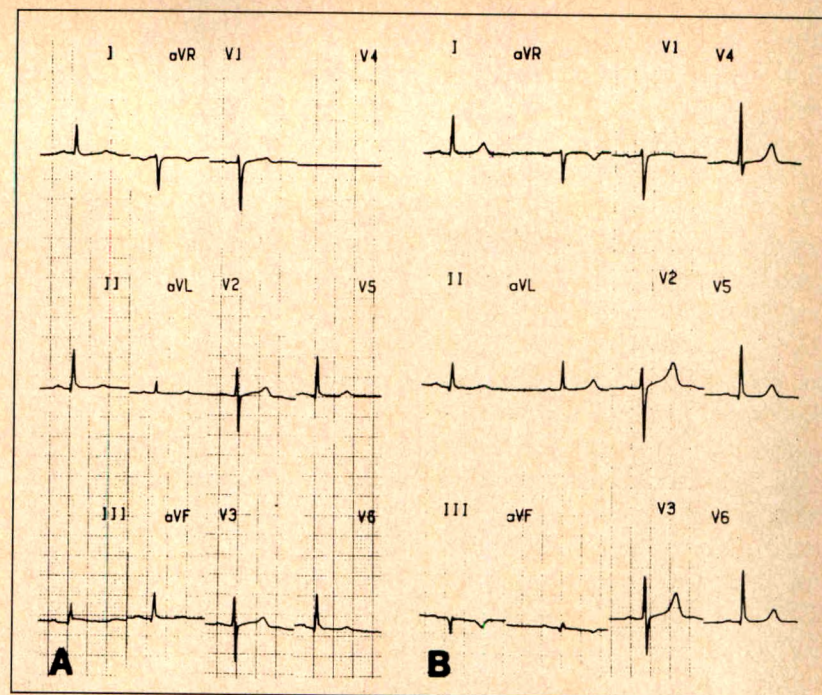


FIGURE 2. A, electrocardiogram obtained from case 2 shortly after the onset of severe chest pain. The slight ST-segment elevations in leads II, III and aVF are new compared with baseline tracing (not shown) (lead V₄ is missing for technical reasons). **B,** electrocardiogram obtained 4 days later. New or deeper Q waves are now seen in leads II, III and aVF; they are accompanied by new T-wave inversions.

studied. Other vasoactive drugs, including nitrates, are well known to have the potential of exacerbating myocardial ischemia by lowering perfusion pressure. Both patients reported here had a decrease in blood pressure that can be expected to have lowered coronary perfusion pressure. This decrease in coronary perfusion pressure represents the simplest explanation for the development of ischemia. In both patients, the restoration of blood pressure did *not* abolish the ischemic event. If *selective* dilatation of resistance vessels occurs, coronary steal may occur, particularly if the resistance vessels supply nonischemic myocardium, while ischemic myocardium is dependent on collateral circulation.^{6,7} Drugs that have a weaker effect on resistance vessels, or that selectively dilate large or collateral vessels, are far less likely to produce coronary steal.⁶ Selective coronary vasodilation is, at least in part, responsible for the increasingly wide use of dipyridamole, as it is used in the dipyridamole-thal-

lium stress test. Dipyridamole is used because its effect on resistance vessels induces a redistribution of coronary flow, capable of producing ischemia by coronary steal.⁸ Niacin and dipyridamole share apparently similar vasodilating properties.⁵ The observation that niacin causes flushing and hypotension in some patients suggests that it acts preferentially on relatively small resistance vessels.⁵ Thus, although not well studied, it appears possible that niacin can act like certain other vasodilators known to create a coronary steal. This would only appear clinically important in patients such as those reported here, with unstable coronary artery disease and collateral-dependent regions of myocardium.⁶ Thus, niacin appears to be capable of promoting ischemia in such patients, either by lowering perfusion pressure, or by creating coronary steal, or by a combination of both actions.

Pretreatment with aspirin limits flushing in many patients receiving niacin; however, both patients de-

scribed in this study had been treated with aspirin, suggesting that such therapy may not prevent the complication described. Use of a long-acting niacin preparation does prevent some of the adverse effects of niacin³ and may have prevented the complications described here.

In view of the possibility that niacin may exacerbate myocardial ischemia, we suggest limiting its immediate use in patients with unstable angina or recent (1 to 2 weeks) myocardial infarction. Although niacin is extremely important as an agent for the management of lipid abnormalities, it need not be prescribed urgent-

ly and its use can be deferred in patients with clinically active coronary artery disease until after they are discharged from the hospital. Based on the experience reported, we often temporarily discontinue niacin in patients who develop acute unstable ischemia, because even if the risk it confers is only slight, niacin's short-term benefit is minimal.

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Mechanical Failure of a St. Jude Medical Prosthesis

David A. Orsinelli, MD, Richard C. Becker, MD, Henri F. Cuénoud, MD, and John M. Moran, MD

The St. Jude Medical (SJM) prosthetic cardiac valve is a low-profile, bileaflet mechanical valve with an excellent record of durability and a low overall complication rate.¹⁻³ Mechanical failure is a rare occurrence with this valve.⁴ We report a case of mechanical failure of a SJM prosthesis due to leaflet fracture with subsequent embolization.

A 26-year-old man was found by cardiac catheterization at age 12 years to have moderate mitral stenosis. He underwent open commissurotomy at age 13 because of

increasing dyspnea. At age 21, atrial fibrillation and congestive heart failure occurred. Cardiac catheterization revealed severe mitral stenosis (mitral valve area = 0.57 cm²) and a left ventricular ejection fraction of 25%. In February 1984, he underwent mitral valve replacement with a 29-mm SJM prosthesis and tricuspid valve anuloplasty. Review of the operative report revealed no evidence of difficulty in seating the prosthesis, but the posterior leaflet did not open fully. No difficulty with valve closure was encountered, and it was believed that normal valve function would occur once the heart was full and beating. The patient did well postoperatively.

The patient was first seen at our institution in October 1988; he had no complaints and physical examination was unremarkable. He pre-

sented several months later with the sudden onset of dyspnea, which began shortly after he'd been playing soccer. Initial evaluation revealed a heart rate of 100 beats/min and a systemic blood pressure of 100/64 mm Hg. Prosthetic mitral valve closure sounds were normal and a grade 2 to 3/6 holosystolic murmur at the cardiac apex that radiated to the axilla was audible. In addition, there was a grade 2/6 holosystolic murmur at the right lower sternal border that radiated to the back and a grade 1/6 diastolic murmur located along the left sternal border. Rales were heard over both lung fields. Chest x-ray was consistent with congestive heart failure. Electrocardiogram revealed sinus tachycardia (rate, 100 beats/min), right axis deviation, and a nonspecific intraventricular conduction delay. A transthoracic echocardiogram demonstrated hyperdynamic left ventricular function, mitral regurgitation of indeterminate severity, and moderate aortic and tricuspid regurgitation. The prosthesis appeared to be well seated. The pro-

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thrombin time was 16 seconds and oxygen partial pressure was 54 mm Hg with 40% oxygen. The patient was initially treated with intravenous diuretics, with a resultant decrease in systemic blood pressure. The blood pressure gradually increased with intravenous fluid administration; intravenous antibiotics and sodium nitroprusside were subsequently begun. He was taken to the cardiac catheterization laboratory: mean right atrial pressure was 1 mm Hg, pulmonary artery pressure 55/25 mm Hg and pulmonary capillary wedge pressure 27 mm Hg, with "V" waves to 50 mm Hg. Cardiac output was 3.95 liters/min (cardiac index, 2.4 liters/min/m²). Left ventriculography revealed severe mitral regurgitation and an ejection fraction of 73%. Fluoroscopy of the mitral valve revealed normal motion of 1 leaflet. The second leaflet moved intermittently and appeared to remain partially open during systole, raising the possibility of a valvular thrombosis.

The patient deteriorated over the next 2 hours and required endotracheal intubation. An intra-aortic balloon pump was also placed and the patient was taken emergently to the operating room. At surgery, the anterior prosthetic leaflet was fractured several millimeters from the hinge points, and >2/3 of the leaflet was missing (Figure 1). The valve was explanted and replaced with a 31-

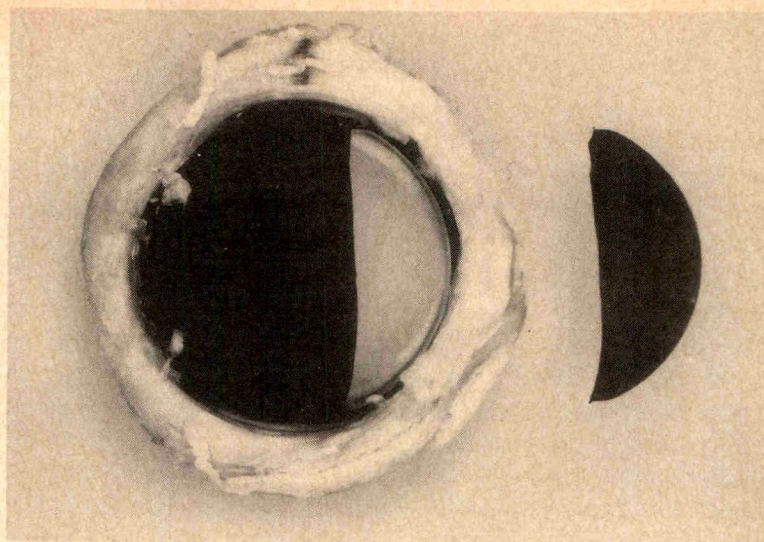


FIGURE 1. Photograph of the explanted valve in the closed position with the embolized leaflet fragment recovered at autopsy.

mm SJM prosthesis without difficulty. The missing fragment of the valve leaflet was not located.

In the early postoperative period, the patient was hemodynamically stable. He developed severe lower extremity edema secondary to bilateral compartment syndromes and was taken to the operating room for bilateral fasciotomies and removal of the intra-aortic balloon pump. Clinical deterioration ensued and a trans-thoracic intra-aortic balloon pump was placed, with improvement in the patient's hemodynamic status. Although he improved clinically in the early postoperative period, he soon developed evidence of bilateral lower extremity muscle necrosis. After nonviable muscle was found in all compartments, above-

the-knee bilateral amputations were performed. The patient remained stable for approximately 12 hours and then had an acute neurologic event, consisting of right hemiplegia followed by progressive obtundation. A computerized tomographic scan revealed marked cerebral edema and brainstem herniation. After consultation with the patient's family, support was withdrawn and the patient died. At postmortem examination, the portion of the original mitral valve leaflet that had embolized was located in the left common iliac artery 2.5 cm distal to the aortic bifurcation.

The present case is the first reported incident of leaflet fracture with the SJM prosthesis. While mechanical failure has been reported,

TABLE 1 Previously Reported Cases of St. Jude's Medical Prosthesis Failure

Author	Age (yr)/Sex	Position/Valve Size	Interval from Implantation to Failure	Clinical Outcome
Odell et al ⁴	17/M	Mitral/27 mm	20 months	Successful reoperation
	12/M	Mitral/25 mm	11 months	—
	27/M	Mitral/31 mm	23 months	—
	27/—	Aortic/—	25 days	Death at reoperation
Burckhardt et al ³	12/M	Mitral/—	10 months	Successful reoperation
Arom et al ² (report from SJM)	—/—	—	—	—

— = no information available.
SJM = SJM Inc.

not infrequently, with certain models of the Björk-Shiley tilting disc prosthesis,⁵ mechanical failure of the SJM valve is rare. Several large series detailing long-term experiences with this valve have been reported.¹⁻³ Arom et al² reported no valve failures in their series but did comment on an unpublished report of leaflet embolization from SJM, Inc. A similar case of leaflet dislocation involving a mitral valve prosthesis was noted by Burckhardt et al³ in 1 patient from a series of 828 valves implanted in 743 patients who were followed for a mean of 2.6 years.

Odell et al⁴ reported the only collective series to date of mechanical failure with the SJM prosthesis. They described a 17-year-old boy in whom an intact leaflet of an SJM prosthesis dislodged, causing acute mitral insufficiency. Valve failure was attributed to cracks in the pivot

guards rather than leaflet fracture. They noted that there had been only 3 other cases of mechanical failure of the SJM prosthesis reported, all due to embolization of intact leaflets. Two of the known cases also involved valves in the mitral position.

Thus, 6 cases of mechanical failure of SJM prosthetic valves have been reported, all due to embolization of intact leaflets. These previously reported cases are summarized in Table I. A careful review of the literature revealed only 3 cases of leaflet fracture in prosthetic valves, 1 in a Lillehei-Kaster mitral valve,⁶ and 2 in Edwards-Duromedics bileaflet valves placed in the mitral position.⁷ Our case represents a unique cause of mechanical failure in the SJM prosthesis: failure due to fracture of a valve leaflet with subsequent embolization of the leaflet fragment.

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Transtacheal Placement and Imaging with a Transesophageal Echocardiographic Probe

Leonard F. Fagan, Jr., MD, Ronald Weiss, MD, Ramon Castello, MD, and Arthur J. Labovitz, MD

Transesophageal echocardiography (TEE) has emerged as a safe and reliable imaging technique for both ambulatory and critically ill patients. The procedure has minimal associated risks and few reported complications, including transient arrhythmias and conduction disturbances, bronchospasm, unilateral vocal cord paralysis related to extreme neck flexion during neurosurgery, hypoxemia in congenital heart disease with right-to-left shunts, and esophageal injury in patients with underlying esophageal pathology.¹⁻⁴ We report a previously undescribed complication of suspected inadvertent endotracheal intubation resulting in transient cyanosis in a patient undergoing TEE.

A 74-year-old man with a history of chronic atrial fibrillation was admitted to the neurology service with a dense right middle cerebral artery infarction, manifested by the acute onset of left hemiplegia, right gaze preference, ptosis, dysarthria and difficulty in swallowing. Physical examination was significant for the absence of soft palate elevation or a gag reflex, consistent with a pseudobulbar palsy. Two-dimensional transthoracic echocardiography was sub-optimal and TEE was requested for evaluation of a possible cardiac source of embolus. The patient was lethargic and unable to cooperate

during the TEE examination. No sedation was given. The patient's hypopharynx was anesthetized with topical lidocaine. With the patient in the left lateral decubitus position, the TEE probe was introduced with finger guidance to a distance of approximately 30 cm from the incisors without difficulty. An attempt to advance the probe was met by resistance for 3 minutes. Initial images were of poor quality despite probe manipulation. Despite unlabored spontaneous respiration, the patient was noted to become cyanotic and the probe was withdrawn. Cyanosis rapidly cleared and the procedure was aborted. To exclude underlying esophageal pathology, the patient was referred for esoph-

agogastrosocopy, which was normal. Later, a feeding tube was placed without difficulty. Although severe esophageal spasm cannot be entirely excluded, the patient's reversible cyanosis and subsequent normal esophageal evaluation make this unlikely. This suggests that the TEE probe was inadvertently advanced into the trachea, facilitated by the patient's pseudobulbar palsy, and that resistance was encountered at or near the carina. The patient's subsequent hospital course was complicated by an aspiration pneumonia and eventually he was transferred to a rehabilitation facility.

To our knowledge, this is the first described case of inadvertent transtracheal intubation and imaging with a TEE probe. Our experience with >500 patients is comparable to that reported by other laboratories,⁵ with unsuccessful TEE probe placement limited to <1% of cases, and

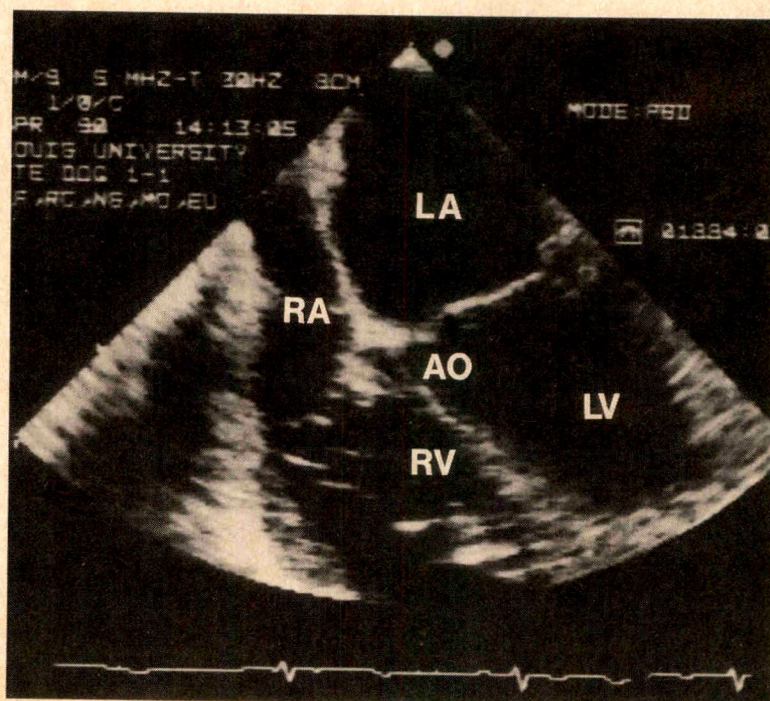


FIGURE 1. Transesophageal echocardiogram of a dog, 5-chamber view. AO = aorta; LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle.

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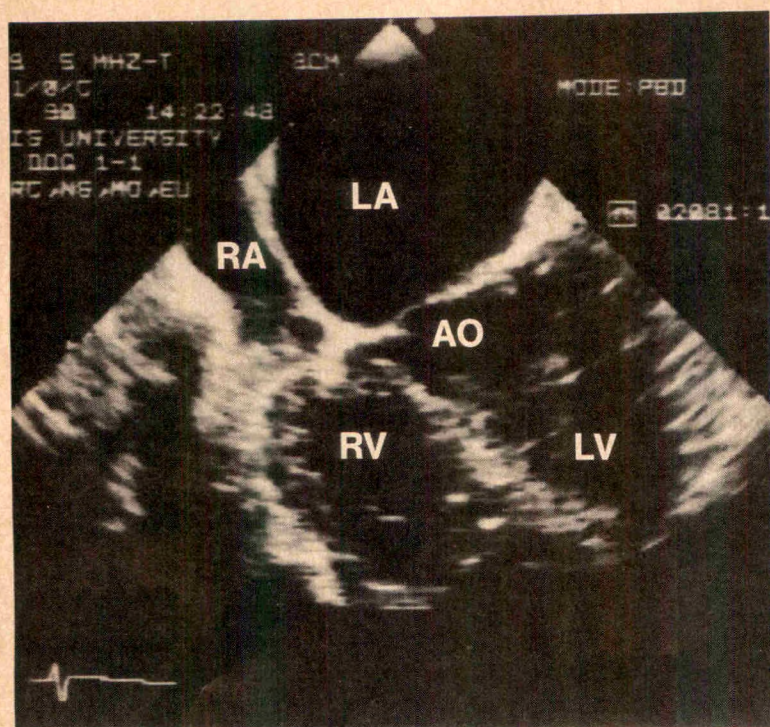


FIGURE 2. Transtacheal echocardiogram of a dog, 5-chamber view. Abbreviations as in Figure 1.

complications limited to transient arrhythmias and bronchospasm.

Because the TEE probe is a modified gastroscope without fiberoptic capability and because direct laryngoscopy was not performed, we can only presume inadvertent endotracheal intubation in this case. In fact, the presence of a possible air interface and cartilage within the trachea would appear to make transtacheal ultrasound imaging very difficult. To evaluate the possibility of transtacheal ultrasound imaging further, a dog model was used.

A 25-pound mongrel dog was sedated with an intravenous barbiturate and an endotracheal tube was placed for delivery of inhalational anesthesia and oxygen by mechanical ventilation. Using a Hewlett-

Packard 27020 (Hewlett-Packard Medical Products Group, Andover, Massachusetts) ultrasound machine with a 5.0-MHz phased array transducer mounted on the tip of a modified gastroscope, we obtained baseline TEE images after probe introduction into the esophagus by finger guidance, with the dog in the left lateral decubitus position (Figure 1). The endotracheal tube was then removed and the probe was placed in the dog's trachea with the aid of a laryngoscope. The probe was advanced until resistance was encountered at approximately 27 cm from the gum line, presumably at the carina, and images were briefly obtained in the apneic dog (Figure 2). The transtacheal image quality was virtually indistinguishable from that

obtained by the transesophageal approach.

Our experience should caution others performing TEE. Particularly when this procedure is performed in patients who have had neurologic events and may be lethargic or without an appropriate gag reflex, adequate airway protection and the possibility of inadvertent endotracheal intubation must be considered. Also, continuous pulse oximetry monitoring is highly recommended. The triad of resistance to probe advancement at approximately 30 cm from the incisors, unusual image orientation or quality, and patient decompensation (cyanosis or oxygen desaturation) should suggest endotracheal TEE probe placement. The use of direct laryngoscopy for probe placement in compromised patients might also be helpful in avoiding this rare potential problem.

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Clarification

The article entitled "Termination of sustained ventricular tachycardia by external noninvasive pacing," published in *The American Journal of Cardiology* in 1988 (61:574-577), of which I was the principal author, states that patients involved in that study gave informed written consent before electrophysiologic testing. That statement was incorrect, in that prior written consent was not obtained for all patients. All patients had, however, given prior oral consent, and I have now obtained written consents for all 8 participants who are living; the remaining 6 have unfortunately died. I did not obtain prior written consent because I incorrectly assumed the external pacing to be an extension of their clinical care. The original data has been reviewed by Dr. David Leaman, the Medical Center's Chief of Cardiology, and he finds no discrepancy with the published article aside from the matter mentioned above.

I regret any inconvenience I have caused my colleagues or the *Journal*.

Jerry C. Luck, MD
Hershey, Pennsylvania
17 October 1990

Diastolic Dysfunction in Prinzmetal's Angina

The elegant Doppler echocardiographic study of Doria et al¹ confirms once again that left ventricular diastolic dysfunction can be not only a pure consequence of myocardial ischemia but can also precede left ventricular systolic abnormalities. Their study differed from previous studies in that previous patient populations included subjects

with multivessel coronary artery disease and previous myocardial infarction who probably had some left ventricular dysfunction at rest. In this study, all patients had normal left ventricular function in the control condition and had insignificant coronary lesions or 1-vessel disease on coronary arteriography.

Thus, the concept of diastolic dysfunction as a mechanism underlying impaired cardiac function is similar to the description of "backward failure" as originally proposed by Hope in 1832.² Similarly, "forward failure," expounded in 1913 by MacKenzie,³ can be equated to systolic dysfunction. Although backward failure and forward failure hypotheses, 2 seemingly opposite views that led to lively controversy during the first half of this century, were both later reconciled to be present in most patients with congestive heart failure, now, toward the end of this century, the pendulum once again swings in the direction whereby diastolic dysfunction can occur without systolic dysfunction. It is clinically important to distinguish diastolic dysfunction in coronary artery disease from systolic dysfunction, as the treatment is quite different.

Tsung O. Cheng, MD
Washington, D.C.
14 November 1990

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2. Hope J. A Treatise on the Diseases of the Heart and Great Vessels. London: Williams-Kidd, 1832.

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Role of Arterial Filters in the Prevention of Systemic Embolization by Microbubbles Released by Oxygenators

In a previous paper¹ we reported our observations on the production of microbubbles by 2 different types of oxygenators during cardio-

pulmonary bypass (CPB). In that study, transesophageal echocardiography was used to detect microbubbles reaching the descending aorta in 20 patients undergoing various types of open-heart surgery. A hollow-fiber oxygenator was used in 10 patients and a bubble oxygenator in the remaining 10. An arterial filter was never used. When bubble oxygenators were used, microbubbles were seen as oblong bright particles with continuous, fast and circular movement in the descending aorta, throughout CPB. Conversely, with hollow-fiber oxygenators, the release of microbubbles was confined to the early phase of CPB, after the infusion of the priming solution.

When commenting on our findings, we proposed the incorporation of an arterial filter in the CPB circuit to "eliminate or significantly decrease the number of oxygenator-generated microbubbles reaching the arterial circulation." We therefore repeated the study in 2 more groups of 10 patients each, using exactly the same methodology and adding an arterial filter of proven efficacy (Pall Ultipor EC 3840) to the circuit.² As expected, we found a great reduction in the number and the size of the microbubbles, which, however, still appeared consistently and had an identical time-course as in the previous study. Specifically, they lasted throughout CPB when bubble oxygenators were used, and disappeared within 2 minutes when hollow-fiber oxygenators were used.

These results are justified by the characteristics of the 40- μ m filters that we used, which allow very small bubbles through, and by the high resolution of the transesophageal probe, permitting their detection. Our experience confirms data obtained with microbubble activity monitors³ and with transcranial Doppler probes,⁴ which also show a significant reduction in the number and size of microbubbles when arterial filters are used.

Although not resolute, arterial filters of the type we used seem helpful in decreasing gaseous microembolism in the systemic circu-

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lation and may therefore minimize its deleterious effects on the central nervous system.^{2,4}

Pietro A. Abbruzzese, MD
Luigi Meloni, MD
Gabriele Cardu, MD
Valentino Martelli, MD
Angelo Cherchi, MD
 Cagliari, Italy
 19 November 1990

1. Meloni L, Abbruzzese PA, Cardu G, Aru GM, Loriga P, Ricchi A, Martelli V, Cherchi A. Detection of microbubbles released by oxygenators during cardiopulmonary bypass by intraoperative transthoracic echocardiography. *Am J Cardiol* 1990;66:511-514.
2. Willner AE, Caramante LL, Garvey JW, Wolpowitz A, Weisz D, Rabiner CJ, Wisoff G. The relationship between arterial filtration during open heart surgery and mental abstraction ability. *Proc Am Acad Cardiovasc Perfusion* 1983;4:56-64.
3. Pearson DT. Microemboli: gaseous and particulate. In: Taylor KM, ed. *Cardiopulmonary Bypass*. London: Chapman and Hall, 1986:313-335.
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We Are a Third of One

I read with interest the From-the-Editor editorial in the October 1, 1990, issue of the *Journal*. The editor stated that animal flesh was

never intended for human beings, who are natural herbivores. However, the editor's smile in the accompanying picture was revealing. I counted 4 upper incisor and 2 upper canine teeth and assumed there were the same number of bottom teeth (not shown). Therefore, 12 of a total of 32 teeth ($>1/3$) are used for piercing and cutting food, i.e., flesh. The remaining teeth, premolars and molars, are used for grinding plant products.

The editor's point is well taken, but humans are not natural herbivores. We are omnivores. A small amount of lean animal flesh daily is permitted on a cholesterol-lowering diet.¹ I agree we should consume proportionally more vegetables, fruits and grains, but there is no evidence that animal flesh in moderation is deadly.

Mark R. Goldstein, MD
 Upland, Pennsylvania
 6 November 1990

1. Report of the National Cholesterol Education Program Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults. *Arch Intern Med* 1988;148:36-69.

REPLY: I enjoyed your Readers' Comments. Just because a group of experts in an organization recommend that "a small amount of lean animal flesh daily . . ." is permissi-

ble for humans does not mean that animal flesh is good for humans. For humans to eat animal flesh is certainly "deadly" to the animals we eat. Yes, most humans can and do eat animal flesh, and yes, some of our teeth are sharp, but these facts do not mean that we should eat meat (and kill animals to do so) and they do not mean that we are natural carnivores. Both human beings and the 100,000 cows, and the 250,000 pigs, and the 9 to 12 million chickens we kill every day in the USA would be better off if human beings did not think we were carnivores.

William C. Roberts, MD
 Bethesda, Maryland
 8 November 1990

Correction

In the study, "Usefulness of Blood Lactate as a Predictor of Shock Development in Acute Myocardial Infarction" by Mavrić et al in the March 15, 1991 issue, part of the address for reprints and the last line of Figure 1 were mistakenly omitted. Here is the full address for reprints, and Figure 1 appears below:

Address for reprints: Žarko Mavrić, MD, Department of Internal Medicine, Division of Cardiology (Coronary Care Unit), Clinical Hospital Center Rijeka, 51000 Rijeka, Croatia, Yugoslavia.

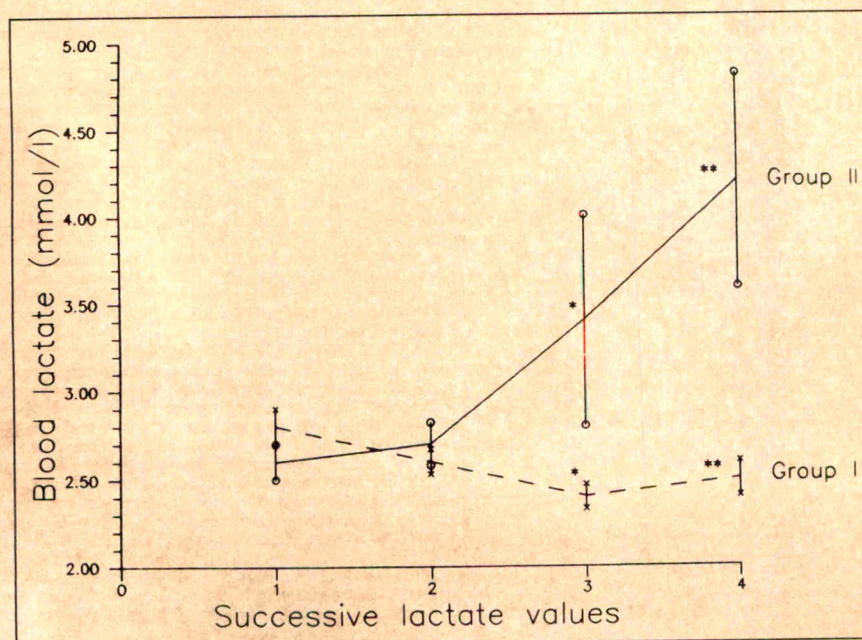


FIGURE 1. Blood lactate values obtained on successive days in 2 groups of patients. Values are expressed as mean \pm standard error of the mean. Group I = patients without shock; Group II = patients who developed shock during hospitalization. * $p < 0.05$; ** $p < 0.001$.

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A Brief Summary follows.

CONTRAINDICATIONS. 1. Hepatic or severe renal dysfunction, including primary biliary cirrhosis.

2. Preexisting gallbladder disease (See WARNINGS).

3. Hypersensitivity to gemfibrozil.

WARNINGS. 1. Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, the adverse findings with clofibrate in two large clinical studies may also apply to gemfibrozil. In the first of those studies, the Coronary Drug Project, 1000 subjects with previous myocardial infarction were treated for five years with clofibrate. There was no difference in mortality between the clofibrate-treated subjects and 3000 placebo-treated subjects, but twice as many clofibrate-treated subjects developed cholelithiasis and cholecystitis requiring surgery. In the other study, conducted by the World Health Organization (WHO), 5000 subjects without known coronary heart disease were treated with clofibrate for five years and followed one year beyond. There was a statistically significant, 29%, higher total mortality in the clofibrate-treated than in a comparable placebo-treated control group. The excess mortality was due to a 33% increase in noncardiovascular causes, including malignancy, post-cholecystectomy complications, and pancreatitis. The higher risk of clofibrate-treated subjects for gallbladder disease was confirmed.

During the Helsinki Heart Study and in the 1½ year follow-up period since the trial was completed, mortality from any cause was 59 (2.9%) in the Lipid group and 55 (2.7%) in the placebo group. Mortality from any cause during the double-blind portion of the study was 44 deaths in the Lipid group and 43 in the placebo group. Because of the more limited size of the Helsinki Heart Study, this result is not statistically significantly different from the 29% excess mortality seen in the clofibrate group in the separate WHO study. Noncoronary heart disease related mortality showed a 58% greater trend in the Lipid group (43 vs 27 patients in the placebo group, $p=0.056$).

In the Helsinki Heart Study, the incidence of total malignancies discovered during the trial and in the 1½ years since the trial was completed was 39 in the Lipid group and 29 in the placebo group (difference not statistically significant). This includes 5 basal cell carcinomas in the Lipid group and none in the placebo group ($p=0.06$; historical data predicted an expected 4.7 cases in the placebo group). GI malignancies and deaths from malignancies were not statistically different between Lipid and placebo subgroups. Follow-up of the Helsinki Heart Study participants will provide further information on cause-specific mortality and cancer morbidity.

2. A gallstone prevalence substudy of 450 Helsinki Heart Study participants showed a trend toward a greater prevalence of gallstones during the study within the Lipid treatment group (7.5% vs 4.9% for the placebo group, a 55% excess for the gemfibrozil group). A trend toward a greater incidence of gallbladder surgery was observed for the Lipid group (17 vs 11 subjects, a 54% excess). This result did not differ statistically from the increased incidence of cholecystectomy observed in the WHO study in the group treated with clofibrate. Both clofibrate and gemfibrozil may increase cholesterol excretion into the bile leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. Lipid therapy should be discontinued if gallstones are found.

3. Since a reduction of mortality from coronary artery disease has not been demonstrated and because liver and interstitial cell testicular tumors were increased in rats, Lipid should be administered only to those patients described in the INDICATIONS AND USAGE section. If a significant serum lipid response is not obtained, Lipid should be discontinued.

4. Concomitant Anticoagulants—Caution should be exercised when anticoagulants are given in conjunction with Lipid. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has stabilized.

5. Concomitant therapy with Lipid and Mevacor® (lovastatin) has been associated with rhabdomyolysis, markedly elevated creatine kinase (CK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure (See Drug Interactions). The use of fibrates alone, including Lipid, may occasionally be associated with myositis. Patients receiving Lipid and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myositis, including serum creatine kinase level determination. If myositis is suspected or diagnosed, Lipid therapy should be withdrawn.

6. Cataracts—Subcapsular bilateral cataracts occurred in 10%, and unilateral in 6.3% of male rats treated with gemfibrozil at 10 times the human dose.

PRECAUTIONS. 1. **Initial Therapy**—Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal. Before instituting Lipid therapy, every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities.

2. **Continued Therapy**—Periodic determination of serum lipids should be obtained, and the drug withdrawn if lipid response is inadequate after 3 months of therapy.

3. **Drug Interactions**—(A) **Lovastatin:** Rhabdomyolysis has occurred with combined gemfibrozil and lovastatin therapy. It may be seen as early as 3 weeks after initiation of combined therapy or after several months. In most subjects who have had an unsatisfactory lipid response to either drug alone, the possible benefit of combined therapy with lovastatin and gemfibrozil does not outweigh the risks of severe myopathy, rhabdomyolysis, and acute renal failure. There is no assurance that periodic monitoring of creatine kinase will prevent the occurrence of severe myopathy and kidney damage.

(B) **Anticoagulants:** CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH LIPID. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS STABILIZED.

4. **Carcinogenesis, Mutagenesis, Impairment of Fertility**—Long-term studies have been conducted in rats and mice at one and ten times the human dose. The incidence of benign liver nodules and liver carcinomas was significantly increased in high dose male rats. The incidence of liver carcinomas increased also in low dose males, but this increase was not statistically significant ($p=0.1$). In high dose female rats, there was a significant increase in the combined incidence of benign, and malignant liver neoplasms. In male and female mice, there were no statistically significant differences

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from controls in the incidence of liver tumors, but the doses tested were lower than those shown to be carcinogenic with other fibrates.

Male rats had a dose-related and statistically significant increase of benign Leydig cell tumors at 1 and 10 times the human dose.

Electron microscopy studies have demonstrated a florid hepatic peroxisome proliferation following Lipid administration to the male rat. An adequate study to test for peroxisome proliferation has not been done in humans but changes in peroxisome morphology have been observed. Peroxisome proliferation has been shown to occur in humans with either of two other drugs of the fibrate class when liver biopsies were compared before and after treatment in the same individual.

Administration of approximately three or ten times the human dose to male rats for 10 weeks resulted in a dose-related decrease of fertility. Subsequent studies demonstrated that this effect was reversed after a drug-free period of about eight weeks, and it was not transmitted to the offspring.

5. **Pregnancy Category B**—Reproduction studies have been performed in the rat at doses 3 and 9 times the human dose, and in the rabbit at 2 and 6.7 times the human dose. These studies have revealed no evidence of impaired fertility in females or harm to the fetus due to Lipid. Minor fetotoxicity was manifested by reduced birth rates observed at the high dose levels. No significant malformations were found among almost 400 offspring from 36 litters of rats and 100 fetuses from 22 litters of rabbits.

There are no studies in pregnant women. In view of the fact that Lipid is tumorigenic in male and female rats, the use of Lipid in pregnancy should be reserved for those patients where the benefit clearly outweighs the possible risk to the patient or fetus.

6. **Nursing Mothers**—Because of the potential for tumorigenicity shown for gemfibrozil in rats, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

7. **Hematologic Changes**—Mild hemoglobin, hematocrit and white blood cell decreases have been observed in occasional patients following initiation of Lipid therapy. However, these levels stabilize during long-term administration. Rarely, severe anemia, leukopenia, thrombocytopenia, and bone marrow hypoplasia have been reported. Therefore, periodic blood counts are recommended during the first 12 months of Lipid administration.

8. **Liver Function**—Abnormal liver function tests have been observed occasionally during Lipid administration, including elevations of AST (SGOT), ALT (SGPT), LDH, bilirubin, and alkaline phosphatase. These are usually reversible when Lipid is discontinued. Therefore periodic liver function studies are recommended and Lipid therapy should be terminated if abnormalities persist.

9. **Use in Children**—Safety and efficacy in children have not been established.

ADVERSE REACTIONS. In the double-blind controlled phase of the Helsinki Heart Study, 2046 patients received Lipid for up to 5 years. In that study, the following adverse reactions were statistically more frequent in subjects in the Lipid group (placebo incidence in parentheses): gastrointestinal reactions, 34.2%

(23.8%); dyspepsia, 19.6% (11.9%); abdominal pain, 9.8% (5.6%); acute appendicitis (histologically confirmed in most cases where data are available), 1.2% (0.6%); atrial fibrillation, 0.7% (0.1%).

Adverse events reported by more than 1% of subjects, but without a significant difference between groups (placebo incidence in parentheses) were: diarrhea, 7.2% (6.5%); fatigue, 3.8% (3.5%); nausea/vomiting, 2.5% (2.1%); eczema, 1.9% (1.2%); rash, 1.7% (1.3%); vertigo, 1.5% (1.3%); constipation, 1.4% (1.3%); headache, 1.2% (1.1%).

Gallbladder surgery was performed in 0.9% of Lipid and 0.5% of placebo subjects, a 64% excess, which is not statistically different from the excess of gallbladder surgery observed in the clofibrate compared to the placebo group of the WHO study.

Nervous system and special senses adverse reactions were more common in the Lipid group. These included hypesthesia, paresthesias, and taste perversion. Other adverse reactions that were more common among Lipid treatment group subjects but where a causal relationship was not established include cataracts, peripheral vascular disease, and intracerebral hemorrhage.

From other studies it seems probable that Lipid is causally related to the occurrence of **musculoskeletal symptoms** (See WARNINGS), and to **abnormal liver function tests** and **hematologic changes** (See PRECAUTIONS).

Reports of viral and bacterial infections (common cold, cough, urinary tract infections) were more common in gemfibrozil-treated patients in other controlled clinical trials of 805 patients.

Additional adverse reactions that have been reported for gemfibrozil are listed below by system. These are categorized according to whether a causal relationship to treatment with Lipid is probable or not established:

CAUSAL RELATIONSHIP PROBABLE: *Gastrointestinal:* cholestatic jaundice; *Central Nervous System:* dizziness, somnolence, paresthesia, peripheral neuritis, decreased libido, depression, headache; *Eye:* blurred vision; *Genitourinary:* impotence; *Musculoskeletal:* myopathy, myasthenia, myalgia, painful extremities, arthralgia, synovitis, rhabdomyolysis (see WARNINGS and Drug Interactions under PRECAUTIONS); *Clinical Laboratory:* increased creatine phosphokinase, increased bilirubin, increased liver transaminases (AST [SGOT], ALT [SGPT]), increased alkaline phosphatase; *Hematopoietic:* anemia, leukopenia, bone marrow hypoplasia, eosinophilia; *Immunologic:* angioedema, laryngeal edema, urticaria; *Integumentary:* exfoliative dermatitis, rash, dermatitis, pruritus.

CAUSAL RELATIONSHIP NOT ESTABLISHED: *General:* weight loss; *Cardiac:* extrasystoles; *Gastrointestinal:* pancreatitis, hepatoma, colitis; *Central Nervous System:* confusion, convulsions, syncope; *Eye:* retinal edema; *Genitourinary:* decreased male fertility; *Clinical Laboratory:* positive antinuclear antibody; *Hematopoietic:* thrombocytopenia; *Immunologic:* anaphylaxis, Lupus-like syndrome, vasculitis; *Integumentary:* alopecia.

DOSAGE AND ADMINISTRATION. The recommended dose for adults is 1200 mg administered in two divided doses 30 minutes before the morning and evening meal.

MANAGEMENT OF OVERDOSE. While there has been no reported case of overdose, symptomatic supportive measures should be taken should it occur.

References: 1. Frick MH, Elo O, Haapa K, et al: Helsinki Heart Study: Primary prevention trial with gemfibrozil in middle-aged men with dyslipidemia. *N Engl J Med* 1987;317:1237-1245. 2. Manninen V, Elo O, Frick MH, et al: Lipid alterations and decline in the incidence of coronary heart disease in the Helsinki Heart Study. *JAMA* 1988; 260:641-651. 3. Nikkila EA: Familial lipoprotein lipase deficiency and related disorders of chylomicron metabolism. In Stanbury J, B. et al. (eds.): *The Metabolic Basis of Inherited Disease*, 5th ed., McGraw-Hill, 1983, Chap. 30, pp. 622-642.

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**RAISES HDL, LOWERS LDL AND TRIGLYCERIDES
DRAMATICALLY REDUCES HEART ATTACK**

240 TOTAL

<35 HDL

Low HDL with elevated LDL and triglycerides: A common denominator of many heart attack victims

Mixed hyperlipidemias—elevated cholesterol and triglycerides—are common among heart attack victims,¹ and nearly two thirds of people who developed myocardial infarction in the PROCAM Trial had a low (< 35 mg/dL) baseline level of HDL cholesterol.² LOPID® (gemfibrozil) is not indicated for the treatment of patients with low HDL cholesterol as their only lipid abnormality.

Raised low HDL 25%

—in patients whose baseline HDL was < 35 mg/dL and median baseline LDL was 186 mg/dL in the landmark Helsinki Heart Study (HHS).³

Reduced heart attack incidence up to 62%*

—in these HHS patients.³ Incidence of serious coronary events was similar for LOPID and placebo subgroups with baseline HDL above the median (46.4 mg/dL).³

LOPID is indicated for reducing the risk of coronary heart disease in type IIb patients with low HDL, in addition to elevated LDL and triglycerides, and who have had an inadequate response to weight loss, diet, exercise, and other pharmacologic agents such as bile acid sequestrants and nicotinic acid.

Contraindicated in patients with hepatic or severe renal dysfunction, including primary biliary cirrhosis, preexisting gallbladder disease, or hypersensitivity to gemfibrozil. LOPID may increase cholesterol secretion into the bile, leading to cholelithiasis. Caution should be exercised when anti-coagulants are given in conjunction with LOPID.

* Defined as a combination of definite coronary death and/or definite myocardial infarction. $P = .013$; 95% CI 13.3-111.5.

A powerful case for

LOPID® 
 BID
 (gemfibrozil) 600-mg
 Tablets

**RAISES HDL, LOWERS LDL AND TRIGLYCERIDES
 DRAMATICALLY REDUCES HEART ATTACK**

References 1. Goldstein JL, Hazzard WR, Schrott HG, Bierman EL, Motulsky AG. Hyperlipidemia in coronary heart disease. I. Lipid levels in 500 survivors of myocardial infarction. *J Clin Invest.* 1973;52:1533-1543. 2. Assmann G, Schulte H. PROCAM-Trial: Prospective Cardiovascular Munster Trial. Zurich: Panscientia Verlag; 1986:8-9. 3. Data on file, Medical Affairs Dept, Parke-Davis.

Please see last page of this advertisement for warnings, contraindications, and brief summary of prescribing information.